JOURNAL OF MEDICINAL FOOD
J Med Food 8 (2) 2005, 125–132

Review

Ginger—An Herbal Medicinal Product with Broad Anti-Inflammatory Actions

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ABSTRACT The anti-inflammatory properties of ginger have been known and valued for centuries. During the past 25 years, many laboratories have provided scientific support for the long-held belief that ginger contains constituents with anti-inflammatory properties. 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 non-steroidal 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 *Zingiber officinale* (family Zingiberaceae) and *Alpina galanga* (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. Identification of the molecular targets of individual ginger constituents provides an opportunity to optimize and standardize ginger products with respect to their effects on specific biomarkers of inflammation. Such preparations will be useful for studies in experimental animals and humans.

KEY WORDS: • ***chemokines*** • ***cyclooxygenase*** • ***cytokines*** • ***ginger*** • ***inflammation***

INTRODUCTION

GINGER (*Zingiber officinale* Roscoe) has a long history of medicinal use.[1,2] In traditional Chinese and Indian medicine, ginger has been used to treat a wide range of ailments including stomachaches, diarrhea, nausea, asthma, respiratory disorders, toothache, gingivitis, and arthritis.[2,3] Today, ginger and its extracts are recommended by herbal practitioners primarily for dyspepsia and the prevention of motion sickness.[4] A number of recent studies have renewed interest in ginger for the treatment of chronic inflammatory conditions. This interest can be traced to the discovery in the early 1970s that non-steroidal anti-inflammatory drugs (NSAIDs) produce their effects by inhibiting the biosynthesis of prostaglandins (PGs).[5] Soon thereafter, ginger was found to contain constituents that inhibit PG synthesis, a finding that provided a sound scientific rationale for its anti-inflammatory effects.[6] Subsequent studies revealed that ginger also contains constituents with pharmacological properties similar to the novel class of dual-acting NSAIDs.[7] Compounds in this class inhibit arachidonic acid metabolism via the cyclooxygenase (COX) and lipoxygenase (LOX) pathways. These compounds have notably fewer side effects than conventional NSAIDs and now are being investigated as a novel class of anti-inflammatory compounds.[8–10]

Results of recent studies summarized in this review have shown that ginger's pharmacological effects on the inflammatory process extend well beyond the inhibition of PG synthesis. These studies uncovered an effect of ginger on the production of cytokines that are synthesized and secreted at sites of inflammation. These molecules have become highly promising targets for the treatment of chronic inflammatory disorders.[11] The preclinical findings on mechanisms by

Manuscript received 12 August 2004. Revision accepted 11 November 2004.

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which ginger produces its effects are complemented by recent clinical trials that support the traditional view that ginger has analgesic and anti-inflammatory properties.[12–15] Results from clinical trials, observational studies, and case reports on the medicinal use of ginger can be found on the Internet.[12] This review contains an account of the scientific data on ginger compiled over the past 25 years. These data strongly support the commonly held view that ginger is a valuable medicinal product for the treatment of chronic inflammatory conditions.

CONSTITUENTS OF GINGER

As is the case with many other herbal preparations, ginger extracts are a complex, multicomponent mixture of biologically active constituents. More than 400 chemical compounds have been isolated and identified in extracts of ginger rhizomes, and new ones are still being detected.[16–19] At present, only a few of them have been evaluated for their pharmacological properties. Current evidence suggests that a subfraction containing the structurally related compounds gingerols, shogaols, and paradols accounts for a major portion of ginger's anti-inflammatory properties. These compounds share an aromatic ketone moiety but differ in the length of their alkyl side chain and the substitution pattern on the side chain. Structure–activity relationship analysis suggests that the presence of the phenolic hydroxy group adjacent to the methoxy group is critical for the inhibition of PG synthesis.[20,21] The relative proportions of gingerols, shogaols, and paradols in ginger extracts are determined by a number of factors, including the geographic origin, the maturity of the rhizomes at the time of harvest, and the method by which the extracts are prepared. Shogaols, dehydrated products of gingerols, are a major component of dried ginger powder. Gingerols are thermally labile because of the presence of a β-hydroxy keto group, which readily undergoes dehydration to form the corresponding shogaols (Fig. 1). Shogaols may be further converted to paradols by hydrogenation. Shogaols and zingerone are found only in small quantities in fresh ginger, but are present in large amounts in stored ginger, suggesting that this conversion takes place during processing and storage. The extent of this conversion is likely to have a significant impact on the health effects of ginger preparations since the two classes of compounds are likely to vary in their bioavailability, pharmacokinetics, and pharmacological properties.

Differences in the methods by which ginger extracts are prepared make it difficult to compare the results of studies from various laboratories. Comparative studies of the pharmacological properties of ginger would be greatly facilitated if extracts would be standardized in reference to a universally accepted, internal constituent. Since the inhibitory effects of ginger on PG synthesis can be attributed to the presence of hydroxymethoxyphenyl compounds (HAPC), it is reasonable to use these compounds as an internal standard. The ginger preparation EV.EXT.77, which is derived from *Z. officinale* Roscoe and *Alpina galanga*, is standardized in reference to HAPC and acetoxychavicol acetate (ACA) compounds. HAPC include all constituents containing the 3-methoxy-4-hydroxyphenyl moiety (mainly gingerols and shagaols). According to analytical certificates, each capsule of EV.EXT.77 contains a minimum of 30 mg of HAPC/ACA in 255 mg of mixed extract complex. Despite the success in tracking the anti-inflammatory activities in chromatographic fractions of ginger extracts,[6,21] no attempts have been made to standardize preparations based on bioactivity. This method would have the advantage that it does not require knowledge of the identity of pharmacologically active constituents.[22] This approach would permit mixtures derived from different sources to be standardized with respect to an accepted biological readout such as inhibition of PG synthesis. Such biological assay would be especially useful if active constituents of ginger exert their anti-inflammatory effects via different pharmacological mechanisms and thus may act synergistically.

GINGER INHIBITS PG BIOSYNTHESIS THROUGH INHIBITION OF COX-1 AND COX-2 ENZYME ACTIVITY

A major breakthrough in inflammation research was the discovery by Vane[5] in 1971 that aspirin and related drugs produce their anti-inflammatory effects by inhibiting the synthesis of PGs. This seminal observation prompted several laboratories to explore whether naturally occurring substances with known anti-inflammatory properties also act as inhibitors of PG synthesis. Kiuchi *et al.*[6] were the first to show that extracts of plants belonging to the Zingiberaceae family inhibit PG synthesis *in vitro*. These investigators subjected extracts of fresh ginger to chromatographic purification and analyzed the resulting fractions for their effect on PG synthesis. They isolated and identified [6]-gingerol and

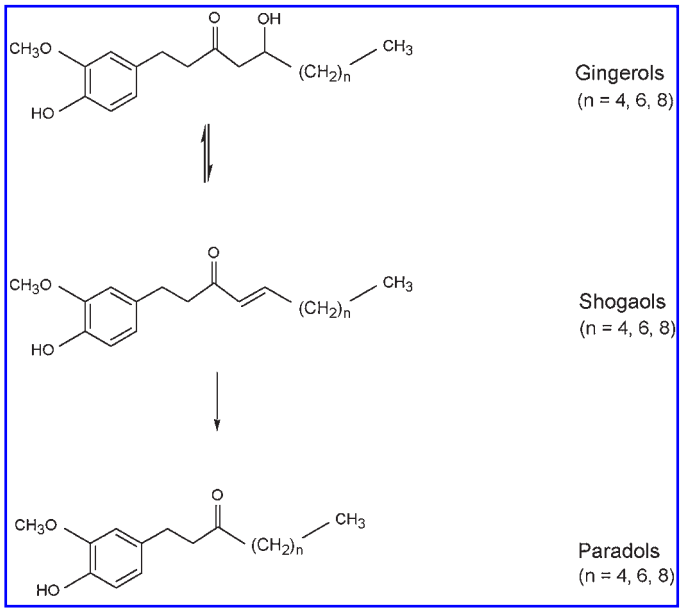

FIG. 1. Chemical structures of some ginger constituents.

four structurally related compounds that inhibit PG synthesis in rabbit renal medulla homogenates with IC_{50} values ranging from 1.0 to 5.5 μM. Under the same assay conditions, indomethacin, one of the most potent inhibitors of PG synthesis, had an IC_{50} value of 4.9 μM. These studies provided the first direct experimental evidence that ginger contains several constituents with anti-inflammatory activities comparable in potency to NSAIDs.

The inhibition of PG synthesis by NSAIDs and ginger is due to inhibition of arachidonic acid metabolism by COX.[23] This enzyme exists in at least two distinct isoforms, designated COX-1 and COX-2.[24] COX-1 is constitutively expressed in nearly all cells and tissues. It regulates important physiologic processes such as gastrointestinal cytoprotection and electrolyte homeostasis in kidneys. In contrast, COX-2 is almost undetectable in most tissues, but its expression is greatly increased at sites of inflammation.[24] It is generally accepted that many of the toxic effects of NSAIDs are due to inhibition of COX-1, while the therapeutic effects reside in the inhibition of COX-2. These observations have led to major efforts by pharmaceutical companies to develop NSAIDs that preferentially inhibit COX-2.[25] So far, only one study has attempted to determine the relative potency of gingerols on COX enzyme activity in intact cells. A study by Tjendraputra *et al*.[20] showed that gingerols are somewhat more potent inhibitors of COX-1 than COX-2, thus identifying them as non-selective COX inhibitors. This was a surprising finding since non-selective NSAIDs are known for their gastrointestinal and renal side effects.[26] In fact, ginger extracts have anti-ulcer activity and are recommended for the treatment of gastrointestinal problems.[26–28] The lack of ginger's gastrointestinal side effects suggested the presence of a yet unidentified pharmacological activity responsible for the protective effects against the toxicity associated with COX-1 inhibition.

GINGER CONSTITUENTS ARE DUAL INHIBITORS OF COX AND 5-LOX

An important advance in the characterization of the anti-inflammatory properties of ginger was the discovery that some of its constituents not only inhibit PG synthesis but also leukotriene (LT) synthesis. LTs are derived from arachidonic acid through the action of the enzyme 5-LOX (Fig. 2). LTs are potent mediators of the inflammatory process and are suspected of playing a key role in the development of gastrointestinal ulcers associated with long-term use of NSAIDs.[29,30] Flynn and Rafferty[7] were the first to show that several ginger constituents are dual inhibitors of arachidonic acid metabolism. Compounds containing the 4-hydroxy-3-methoxyphenyl moiety, including [6]-gingerol, shagaol, gingerdione, and dihydroparadol, inhibit PG and LT production in human neutrophils in the low micromolar range. This observation prompted Flynn and Rafferty[7] to designate some ginger constituents as functional dual inhibitors of COX and LOX. Kiuchi *et al*.[21] found gingerols with long alkyl side chains ($n > 6$; see Fig. 1) to be more potent inhibitors of LT synthesis than of PG synthesis. The significance of this observation was not fully appreciated until the recent discovery that dual inhibitors of COX and LOX are more effective and have fewer gastrointestinal side effects than pure COX inhibitors.[8,10] Nickerson-Nutter and Medvedoff[31] showed that inhibitors of PG and LT synthesis in combination are more effective in preventing collagen-induced arthritis in animals than inhibitors of either class of compounds alone. Unlike ginger, NSAIDs do not inhibit the synthesis of LTs from arachidonic acid. Consequently, COX inhibition by NSAIDs shifts arachidonic acid metabolism to the LOX pathway, leading to an increased production of LTs.[32] Compounds with this dual effect on COX and LOX are being evaluated as a new class of anti-inflammatory drugs.[8–10] The observation that constituents of ginger are dual COX/LOX inhibitors may explain why even high doses of ginger extract do not produce the side effects often observed with non-selective COX inhibitors.

GINGER HAS A HISTORY OF USE FOR THE TREATMENT OF RHEUMATISM

Several clinical studies support the value of ginger for the treatment of arthritis. In addition to alleviating pain, ginger extract has been reported to decrease joint swelling.[33,34] In an exploratory trial of 57 osteoarthritic cases the ginger extract EV.EXT.33 prepared from the rhizomes of *Z. offici-*

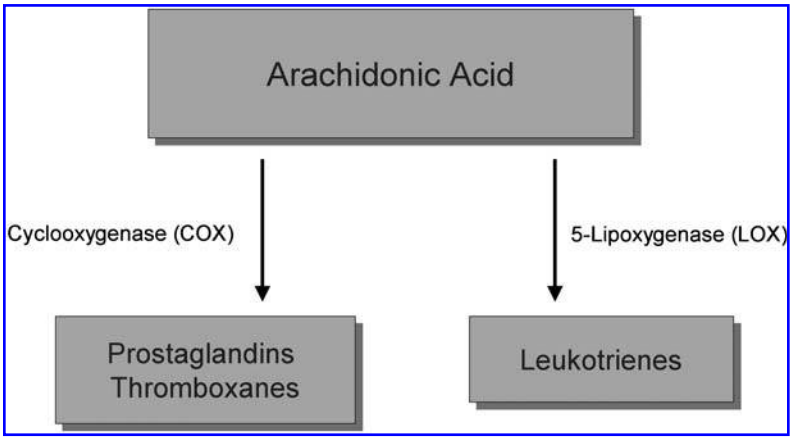

FIG. 2. Arachidonic acid is metabolized via two separate pathways: Metabolism along the COX pathway leads to the formation of PGs and thromboxanes, while metabolism along the LOX pathway leads to the formation of LTs.

nale was reported to be better than placebo during the first period of treatment before cross-over with NSAIDs.[14] Altman and Marcussen[13] using a similar ginger extract (EV.EXT.77) conducted a 6-week, double-blind placebo-controlled parallel group study involving 247 patients with osteoarthritis and demonstrated a statistically significant reduction in knee pain. Their analysis of secondary efficacy variables also showed a consistently superior response in patients treated with ginger extract compared with the control group. Another 6-month, double-blind placebo-controlled study of 29 osteoarthritic patients evaluated the ginger extract Zintona EC derived from *Z. officinale*; this study also observed significantly reduced knee pain compared with controls.[15] These recent clinical studies confirm the beneficial effects of ginger extracts in the treatment of arthritis and inflammation.

GINGER EXTRACT INHIBITS CYTOKINE AND CHEMOKINE INDUCTION IN SYNOVIOCYTES AND CHONDROCYTES—IMPLICATIONS FOR THE TREATMENT OF ARTHRITIS

Genes encoding pro-inflammatory cytokines are up-regulated in chronic inflammatory conditions. Cytokines are a class of small proteins that are secreted at sites of inflammation principally by lymphocytes, macrophages, and fibroblasts. They function as chemical messengers between cells involved in immune and inflammatory responses. Chemokines are a subset of cytokines that act primarily as chemoattractants by inducing the recruitment of effector cells to sites of tissue damage. Inhibiting the production of pro-inflammatory cytokines or blocking their actions is a new and successful therapeutic approach for the treatment of inflammatory disorders,[11] most notably rheumatoid arthritis.[35] Several studies have shown that a number of natural products also contain constituents capable of inhibiting cytokine induction in cells.[36] For example, the flavonoid wogonin inhibits inflammatory activation of microglial cells in culture by diminishing lipopolysaccharide (LPS)-induced tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, and nitric oxide induction.[37] Chang *et al*.[38] demonstrated that wogonin inhibits monocyte chemotactic protein-1 gene expression in human endothelial cells. Some natural products of the terpenoid family have been reported to suppress inflammatory processes via inhibition of the production of TNF-α and IL-1β.[39–41] Several products are available or are currently under development for controlling the adverse effects of TNF-α and IL-1β overproduction in rheumatoid arthritis. These include diacerein, a drug with IL-1 inhibitory activity *in vitro*,[42] etanercept, a TNF-α receptor fusion protein that competitively inhibits the binding of TNF-α to its receptor, and infliximab, a monoclonal antibody that blocks human TNF-α receptors.[11,35]

Osteoarthritis is associated with a variable degree of inflammation. Activation of synovial cells in joints leads to the release of TNF-α and IL-1β.[43] To determine whether a ginger extract can inhibit the induction of pro-inflammatory cytokines, we have conducted a series of experiments in human synoviocytes and chondrocytes.[44,45] Synoviocytes obtained during arthroplasty from osteoarthritic patients were activated with either TNF-α or IL-1β, the two key cytokines involved in the inflammation and degradation of joints. Ginger extract inhibited the expression of TNF-α in synoviocytes activated by either IL-1β or TNF-α at the transcript (Fig. 3) and protein levels.[46] Similarly, ginger extract suppressed TNF-α expression in activated chondrocytes.[45] The ginger extract also inhibited the induction of genes encoding chemokines: monocyte chemotactic protein-1 and interferon-γ inducible protein-10 (see Fig. 3).[47]

In addition to induction of cytokines and chemokines, COX-2 protein levels are also greatly increased in inflamed joint tissue because of COX-2 gene induction.[48] Overexpression of COX-2 is a characteristic feature of osteoarthritis,[49] rheumatoid arthritis,[50] and a number of other pathological conditions such as artherosclerosis, inflammatory

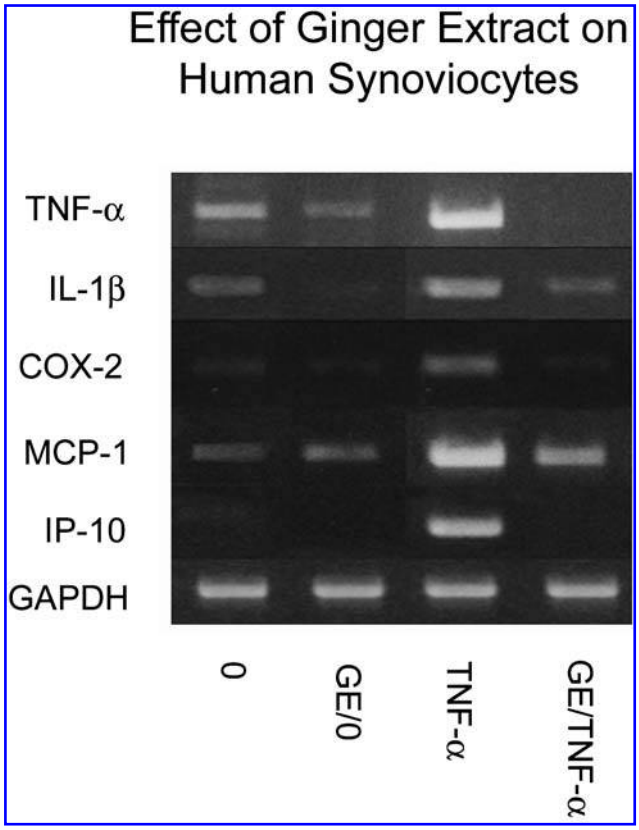

FIG. 3. Inhibition of cytokine and chemokine induction by ginger extract (GE) in human synoviocytes. Synoviocytes were incubated for 1 hour with media in the absence (lane 1) or presence of 100 μg/mL of GE (lane 2). Non-activated human synoviocytes express moderate levels of TNF-α and low levels of IL-1β. When treated with TNF-α (1 ng/mL) for 1 hour, synoviocytes in media alone showed increased levels of TNF-α and IL-1β mRNA (lane 3). These increases were not observed in cultures of synoviocytes pretreated with GE (lane 4). GAPDH, glyceraldehyde phosphate dehydrogenase; IP-10, interferon-γ inducible protein-10; MCP-1, monocyte chemotactic protein-1.

bowel disease, and certain types of tumors.[51,52] The observation that COX-2 is up-regulated in pathological conditions make suppression of COX-2 induction an obvious target. As illustrated in Figure 3, the ginger extract used in this study also prevents the induction of COX-2 in human synoviocytes. Thus, ginger extracts inhibit COX-2 not only at the enzyme level as described above but also at the transcriptional level.[46] The identity of the constituents responsible for these newly described effects remains to be determined. Preliminary experiments with [6]-gingerol indicate that this compound is not a likely candidate since it is only a weak inhibitor of LPS-induced cytokine induction in monocytic THP-1 cells (C.G. Frondoza *et al*., unpublished data). This is in line with the finding of an approximately 1,000-fold difference in the concentrations of sodium salicylate and aspirin needed to inhibit COX-2 enzyme activity and to inhibit COX-2 induction by LPS.[53,54] If this initial observation can be confirmed, it would indicate that the anti-cytokine effects of ginger might not be due to the presence of gingerols.

GINGER AND HUMAN MONOCYTIC CELL ACTIVITY

A common pathological feature of neurodegenerative diseases is the concomitant inflammatory response in the central nervous system.[55–58] This inflammatory response is an intrinsic defense mechanism mediated primarily by microglial cells. In healthy brains, these cells reside in a resting state. In pathological conditions, microglial cells undergo transformation into a cell type endowed with cytotoxic and phagocytic capabilities. This transformation is characterized by changes in the expression of the genes encoding TNF-α and IL-1β. Activated microglial cells have been observed in Alzheimer's disease[59] and Parkinsons's disease[60] and in brains of elderly individuals without apparent neuropathology or signs of neurological deficits.[61–63] Activation of microglial cells is usually a transient event designed to allow tissue repair. Chronically activated microglial cells are suspected to contribute significantly to the neuron loss in neurodegenerative diseases. This conclusion is supported by epidemiological studies documenting that long-term use of NSAIDs significantly reduces the incidence of Alzheimer's disease.[64,65] Currently, the National Institute on Aging is sponsoring a prospective clinical trial (The Alzheimer's Disease Anti-Inflammatory Prevention Trial) to determine whether the NSAIDs can delay or prevent the onset of Alzheimer's disease. Patients enrolled in this clinical trial are cognitively normal individuals with a family history of the disease or age-related memory loss (Study ID Numbers IA0026 and U01-AG15477; NML identifier NCT 00007189).

In a pilot study, Grzanna *et al*.[66] tested the effects of the ginger extract EV.EXT.77 on THP-1 cells to determine whether it can block the induction of pro-inflammatory cytokines in these cells. THP-1 cells, a human monocytic cell line that is widely used as a surrogate for microglial cells, were exposed to an activator, TNF-α, IL-1β, or LPS, in the presence or absence of ginger extract. Figure 4 depicts the increase in mRNA in these cells in response to pro-inflammatory stimuli. Pretreatment of THP-1 cells with ginger extract reduced or completely prevented gene induction (Fig. 4). Message levels of the housekeeping gene glyceraldehyde phosphate dehydrogenase remained unchanged. The results of this study suggest that the anti-inflammatory properties of the ginger extract are not restricted to synoviocytes and chondrocytes but can also be observed in other cell types. In view of the suspected beneficial effects of anti-inflammatory agents regarding the onset and progression of Alzheimer's disease,[67] ginger may provide beneficial effects similar to those of currently used COX inhibitors.

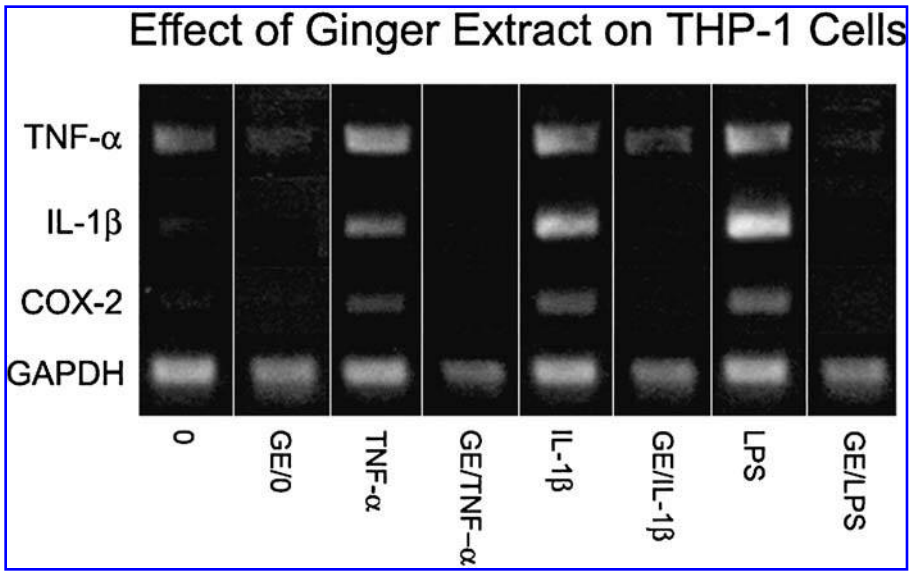

FIG. 4. Ginger extract (GE) inhibits THP-1 cell activation by TNF-α, IL-1β, or LPS. Cells were preincubated with GE (10 μg/mL) or medium alone for1 hour. Thereafter, TNF-α (1 ng/mL), IL-1β (10 ng/mL), or LPS (20 ng/mL) was added, and cells were incubated for an additional hour. Cell pellets were assayed for cytokine, chemokine, and COX-2 mRNA. Unstimulated THP-1 cells showed moderate levels of TNF-α mRNA, while message levels for IL-1β and COX-2 were undetectable (lane 1). Incubation of unstimulated THP-1 cells with GE produced a slight decrease in the levels of TNF-α (lane 2). Exposure of THP-1 cells to TNF-α (lane 3), IL-1β (lane 5), or LPS (lane 7) resulted in an increase in mRNA levels of TNF-α, IL-1β, and COX-2. These increases were blocked when THP-1 cells were pretreated with GE before addition of the stimulating agents (lanes 4, 6, and 8, respectively). The housekeeping gene glyceraldehyde phosphate dehydrogenase (GAPDH) served as a control.

GINGER INHIBITS THE TRANSCRIPTION FACTOR NUCLEAR FACTOR-κB (NF-κB)

NF-κB is a principal regulator of pro-inflammatory gene expression.[68] These include genes encoding cytokines, chemokines, and the enzyme COX-2.[69] Activated NF-κB can be detected at sites of inflammation, and a link among NF-κB activation, cytokine production, and inflammation is now generally accepted.[70] Aberrant NF-κB activation has been observed in synovial tissues of both osteoarthritis and rheumatoid arthritis[71] and in several other chronic inflammatory diseases.[72] NF-κB-directed therapies have been shown to be effective in several animal model of inflammatory diseases.[70] A number of natural products known for their anti-inflammatory properties are now suspected to produce their effects through inhibition of the NF-κB pathway.[36] Several naturally occurring phenolic compounds including curcumin and flavonoids have already been shown to inhibit NF-κB. Based on the observation that ginger extract inhibits pro-inflammatory gene expression, Frondoza *et al*.[46] tested the effect of the ginger extract EV.EXT.77 on NF-κB expression *in vitro*. The results show that this ginger extract significantly inhibits NF-κB expression in activated synoviocytes at 100 μg/mL. Such a mechanism would offer an explanation for the broad effect of ginger on inflammatory processes in various cell types and tissues.

GINGEROLS AS VANILLOID RECEPTOR AGONISTS—A NOVEL MECHANISM FOR GINGER'S EFFECT ON PAIN

The chemical mediators released by local or recruited cells stimulate nociceptive primary afferents at sites of inflammation resulting in pain.[73,74] Joint inflammation in chronic arthritis leads to hyperalgesia, a state characterized by an excessive response to noxious stimuli. PGs, TNF-α, IL-1β, IL-6, and IL-8 all contribute to acute and chronic pain associated with inflammation. NSAIDs are effective in the management of inflammation-related pain. Similarly, the effects of ginger in reducing joint pain are also likely to be mediated through its effect on PG synthesis and other inflammatory mediators. Recently, a novel molecular target of ginger constituents was identified, suggesting an additional mechanism by which ginger may reduce inflammatory pain. Dedov *et al*.[75] reported that gingerols act as agonists at vanilloid receptors. These receptors had previously been identified as receptors activated by capsaicin and are suspected to be present on pain afferents mediating joint pain.[76] Vallinoid receptor agonists are potent analgesics, and the finding by Dedov *et al*.[75] has added gingerols and zingerone to the list of vanilloid receptor agonists. The discovery that ginger constituents function as agonists at vanilloid receptors provides a new mechanistic explanation for the well-documented analgesic effect of ginger in the treatment of pain in rheumatic and inflammatory conditions.

CONCLUSION

A considerable body of scientific data supports the long-held view that ginger has a broad spectrum of anti-inflammatory activities. The scientific data reviewed here show that ginger produces its anti-inflammatory effects through multiple mechanisms. Ginger shares with NSAIDs the property of inhibiting PG synthesis. Some ginger constituents are dual inhibitors of COX and LOX, and thereby reduce the biosynthesis of both PGs and LTs. This remarkable property distinguishes ginger from conventional NSAIDs and may account for its lack of gastrointestinal and renal side effects. The recently discovered anti-cytokine effects of ginger show that the anti-inflammatory properties of this commonly used herb are far from being fully characterized. The identity of the constituents accounting for ginger's anti-cytokine effects remains to be determined. Future studies will need to address the question whether the anti-inflammatory effects of ginger so well documented in *in vitro* experiments can be verified in animals and humans. The results of clinical studies conducted so far have been encouraging. Considering the broad spectrum of ginger's anti-inflammatory actions and its safety record, this herbal product is likely to be a valuable dietary supplement in the treatment of inflammatory disorders.

ACKNOWLEDGMENTS

Some of the experiments reviewed here were supported by a grant from the National Cancer Institute, National Institutes of Health and by Ferrosan A/S.

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