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ANTI-INFLAMMATORY ACTIVITY OF GINGER RHIZOME EXTRACT IN CARRAGEENAN-INDUCED PAW OEDEMA

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Abstract

Ginger rhizome is widely reported to have anti-inflammatory properties, and the carrageenan-induced rat paw oedema test is the model most often used to show it. This review summarises the published literature on that topic. It describes the phases and mediators of carrageenan oedema, the chemistry and variability of ginger extracts, the effects reported for crude extracts and for gingerols and shogaols, and the mechanisms proposed, mainly inhibition of prostaglandin synthesis and cytokine signalling. Evidence points to a real but modest effect. Poorly characterised extracts, small groups and weak reporting limit confidence. No new animal data are presented.

1. INTRODUCTION

Ginger has been in the kitchen and the medicine cabinet for so long that its reputation arrives before any evidence does. The rhizome of *Zingiber officinale* Roscoe is used across Asia, Africa and Europe for nausea, colds, muscle aches and joint pain, and a large experimental literature has grown up around its supposed anti-inflammatory properties [1, 2, 3]. Much of that literature relies on a single, old and well-liked assay: swelling of the rat hind paw after an injection of carrageenan. The test is quick and cheap, and responds to most of the drugs already known to work, which is both its attraction and its limitation.

This review gathers what has been published on the anti-inflammatory activity of ginger rhizome extract in carrageenan-induced paw oedema. It is a narrative synthesis of work by other groups. No animals were used for this article and no new experimental results are reported. The aim is to describe how the

model works, what ginger extracts and their constituents have been reported to do in it, which mechanisms are proposed, and where the evidence is weak, so that a reader planning or judging such an experiment knows what to look for [4, 5].

Ginger is a perennial herbaceous plant, cultivated in India, China, Nigeria and many other tropical countries, and the underground rhizome is the part used in food and medicine. In traditional systems such as Ayurveda and traditional Chinese medicine it is used fresh, dried or processed, often with the aim of treating cold, pain and digestive problems [1, 3]. The range of traditional uses is a reason for the interest, but it also means that claims arise from many different preparations and settings, and bundling them under one name can mislead. Two cautions apply throughout. Ginger extracts are chemically variable, so findings with one preparation do not automatically carry over to another. And a reduction in paw swelling in a rat shows that something has interfered with an acute inflammatory pathway, not that the preparation would help a person with arthritis [6, 7]. Where the text draws a conclusion that depends on only one or two studies, it says so.

2. THE CARRAGEENAN PAW OEDEMA MODEL

The model was described in the early 1960s as a screening method for anti-inflammatory drugs. A small volume of carrageenan, a sulphated polysaccharide from red seaweed, is injected under the plantar skin of the hind paw, and swelling is followed with a plethysmometer or by measuring paw thickness at set intervals over several hours [4, 5]. Treatment is usually given orally or intraperitoneally before the injection, and the effect is expressed as percentage inhibition of the increase in paw volume compared with a vehicle group. A reference drug, most commonly indomethacin or diclofenac, is run alongside.

The swelling develops in phases. An early phase in the first hour or so is associated with release of histamine and serotonin and with increased vascular permeability. A later phase, peaking at around three to five hours, involves bradykinin, prostaglandins and infiltration of neutrophils, with nitric oxide and cytokines contributing [8, 9, 10]. The distinction matters, because a compound that acts only in the later phase is behaving like a cyclooxygenase inhibitor, while activity throughout the time course suggests broader effects. Many papers report only a single time point and so cannot make this distinction.

Mouse versions of the assay exist and behave similarly, though the response depends on age and body weight, and the expression of inducible nitric oxide synthase and cyclooxygenase-2 differs between phases [11]. Inhibitors of nitric oxide synthase reduce swelling in the rat, which shows that the model is not a purely prostaglandin-driven one [10, 12]. For a natural extract, then, observing inhibition does not by itself indicate which mediator is affected. Reference drugs and controls are the foundation of a meaningful comparison. Indomethacin and diclofenac inhibit cyclooxygenase and produce clear inhibition of the late phase, whereas drugs acting on histamine or serotonin are more effective earlier, so a panel of references allows some characterisation of a test material [4, 9, 13]. A vehicle control matched to the extract is essential, since oils and suspending agents can change absorption and, in some cases, produce mild effects of their own. Papers that give the vehicle composition and volume make results far easier to evaluate [5, 14].

Technical details influence results. Carrageenan type (lambda is the commonly used form), concentration, injection volume and depth, room temperature, the time of day and the skill of the operator all matter, as do animal strain, sex and fasting [14, 15]. Blinded measurement is rarely described, even though paw volume readings involve a subjective judgement about where the marker line on the ankle sits. Discussions of replacement, reduction and refinement ask for humane end points and justified group sizes to be reported, but compliance in this older literature is incomplete [16].

Ethical considerations are part of the model's story. Carrageenan injection causes local swelling and pain that is mild to moderate in rats, and the principle of the 3Rs (replacement, reduction and refinement)

applies in full: group sizes should be justified, humane end points set, and observation periods no longer than needed [5, 16]. In vitro assays of cyclooxygenase inhibition or macrophage cytokine release can narrow down candidates before any animal is used, and some groups now use them as a first step, saving animals for compounds that merit it. Such a staged approach also encourages early chemical characterisation of whatever is being tested.

3. GINGER RHIZOME: COMPOSITION AND EXTRACTS

The pungent and bioactive components of fresh ginger are mainly the gingerols, phenolic ketones with a side chain of varying length, of which [10]-gingerol is the most abundant. When the rhizome is dried or heated, gingerols lose water and become shogaols, which are more pungent and, in several assays, more potent [17, 18]. Zingerone arises from further breakdown, and a volatile oil rich in sesquiterpenes such as zingiberene gives ginger its smell [1, 19]. The composition therefore depends on the cultivar, the age at harvest, drying and storage as much as on the species name.

Preparations differ even more. Studies have used aqueous decoctions, ethanolic and methanolic extracts, hexane or ethyl acetate fractions, supercritical carbon dioxide extracts and the essential oil, and they dose them in grams per kilogram of crude extract without always stating the content of marker compounds [19, 20]. A water extract with little gingerol content cannot be compared with an ethyl acetate fraction concentrated in it. Standardisation to a stated percentage of gingerols, determined by high-performance liquid chromatography (HPLC), would allow results to be compared, and the better papers provide it [17, 20].

Stability of the active constituents is a practical problem for extract preparation. Gingerols are heat- and acid-labile and are converted to shogaols during drying or prolonged extraction at high temperature, and shogaols may then degrade further on storage [17, 19]. An extract made from fresh rhizome by cold ethanol will therefore contain a different balance from one prepared by boiling dried powder in water. Papers that do not state the extraction temperature, time and solvent ratio leave out information that a reader needs for any attempt at replication [17, 20]. Authentication of the plant material is a further, unglamorous requirement. Voucher specimens, botanical identification, the source of the rhizome and the extraction yield are reported inconsistently, and adulterated or mislabelled products are known in the market for herbal materials [1, 6]. Because extraction methods also change what is in the extract, the first line of a methods section in a good paper reads as a short chemical description of what was administered, not as a statement that ginger was used.

4. REPORTED ANTI-INFLAMMATORY ACTIVITY

Early work by Mascolo and colleagues reported that ethanolic ginger extracts given to rats reduced carrageenan-induced oedema, in addition to affecting other models such as gastric lesions and diarrhoea, and the result set the pattern for later studies [21]. Subsequent investigations have used a range of preparations. Oral ginger extracts and fractions reduced paw swelling in a dose-related manner in several reports, with inhibition at the later time points usually larger than at the early ones [22, 23]. The percentage inhibition is often reported as comparable to a standard drug at a stated dose, though comparisons between papers are not straightforward.

Comparison with a reference drug is the usual way of judging magnitude. Indomethacin at a few milligrams per kilogram typically produces large inhibition of late-phase oedema, and ginger preparations at much higher doses are often reported to reach a fraction of that effect or, in some papers, to match it [4, 23]. Those statements depend heavily on the dose chosen for the reference. Because the potency difference between a purified drug and a crude extract is expected to be large, what matters for ginger is whether it shows a reproducible, dose-related effect, and not whether it equals an NSAID.

Work on isolated compounds helps to show where activity may lie. [10]-Gingerol given to

rats reduced carrageenan oedema and showed analgesic effects in other tests in a study from Taiwan, and comparative work on [10]-, [15]- and [14]-gingerol and [10]-shogaol indicated that the shogaol and the longer-chain gingerols were stronger in several antioxidant and anti-inflammatory assays [24, 25]. The advantage of shogaols over gingerols has also been described in cell studies of inflammatory mediators [18]. These data suggest that processing which converts gingerols to shogaols could raise potency.

Findings from the principal paw oedema studies and related experimental work on ginger are brought together in table 1. Where activity was reported, the typical pattern was inhibition of swelling over several hours after the carrageenan injection, with preparations richer in pungent compounds doing better. Entries are grouped by the kind of evidence to give an overview in fig. 1. The table is qualitative on purpose, because dose, units and measurement times differ so much from paper to paper.

Table 1: Published findings on ginger, the carrageenan model and related evidence

Topic	Reported finding or feature	Ref.
Carrageenan paw oedema model origin	Biphasic swelling; early histamine and serotonin phase, later prostaglandin and neutrophil phase.	[4, 8, 9]
Nitric oxide model mediator	Synthase inhibitors reduce swelling in both phases, so model is not purely prostaglandin-driven.	[10, 12]
Reporting standards animal studies	Randomisation, blinding and measurement details often missing in older paw oedema reports.	[14, 16]
Ginger rhizome crude extract	Ethanolic extract reduced carrageenan oedema in rats in early ethnopharmacological work.	[21]
Ginger extracts oral dosing	Dose-related reduction of paw swelling, mostly in the later phase of the response.	[22, 23]
[6]-Gingerol isolated compound	Reduced carrageenan oedema and showed analgesic activity in rodents.	[24]
Gingerols and shogaols comparison	Shogaol and longer-chain gingerols stronger in antioxidant and anti-inflammatory assays.	[18, 25]
Cyclooxygenase prostaglandin output	Ginger constituents inhibit COX-2 and lower prostaglandin E2 production in cells.	[20, 26, 27]
Macrophages cytokines	[6]-Gingerol lowered production of pro-inflammatory cytokines in stimulated macrophages.	[28, 29]
Knee osteoarthritis human trials	Modest pain benefit with heterogeneity between trials.	[7, 30]
Pain and exercise human trials	Small effects on pain; systematic reviews cautious about overall conclusions.	[31, 32]

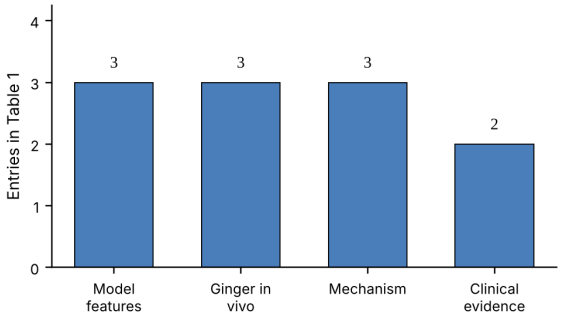


Fig. 1: Number of entries in table 1 by type of evidence

Time course and dose are central to interpreting these data and are often under-reported. In studies that followed the paw for five or six hours, the greatest inhibition by ginger preparations tended to appear at the third to fifth hour, matching the prostaglandin-rich phase [8, 22]. Where only one measurement was made, the choice of time point could make a preparation look strong or weak. Dose ranges also differ, from low tens to several hundred milligrams per kilogram, and full dose-response curves, which would reveal potency and plateau, are given by relatively few authors [21, 23].

Dried and fresh ginger may differ in what they offer. Some comparative work suggests that cooked or dried ginger, richer in shogaols, was more active against inflammatory mediators in cell models than fresh ginger rich in gingerols [18, 25]. Whether the same holds in the rat paw is not

well documented, and the drying temperature used to make the material is rarely recorded, and few studies have compared forms of ginger within the same carrageenan experiment. The point is more than academic, since it bears on which kind of ginger a consumer should choose, if the extract findings were ever to guide advice.

Other models give a consistent, if less detailed, impression. Ginger and ginger oil reduced swelling in arthritis models in rats, and extracts lowered production of prostaglandin E_2 and other inflammatory mediators in cell systems stimulated with lipopolysaccharide [20, 28, 29]. The agreement between models strengthens the case that ginger has real anti-inflammatory properties. However, many positive reports come from related laboratories and from preparations that have not been standardised, which weakens how far the agreement can be pushed.

Negative or weak findings do appear, though less often. In some experiments low doses did nothing, and the water extracts of dried ginger were less active than more lipophilic ones [19, 21]. Since negative results are less likely to be published, the literature probably overstates the typical effect size, a pattern known from other areas of preclinical research. A funnel of small, positive, single-laboratory studies is exactly what this bias would produce, and it is difficult to rule out here.

5. PROPOSED MECHANISMS

The best-supported mechanism is inhibition of arachidonic acid metabolism. Gingerols and diarylheptanoids from ginger inhibited prostaglandin and leukotriene biosynthesis in early work, and later studies showed suppression of cyclooxygenase-2 (COX-2) in intact cells and reduced prostaglandin E_2 (PGE_2) output [20, 26, 27]. Cyclooxygenase inhibition is also the mechanism of aspirin-like drugs, so the finding fits the later phase of the paw oedema curve [8, 13]. Dual effects on the lipoxygenase pathway might give ginger a profile slightly different from that of a classical anti-inflammatory drug.

Cytokine and signalling effects have also been proposed. [10]-Gingerol reduced production of tumour necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β) and interleukin 12 by stimulated macrophages in culture, and extracts inhibited nuclear factor kappa B (NF-κB) activation in some systems [23, 28, 29]. Antioxidant actions, including scavenging of free radicals and support for endogenous defences, may contribute, since reactive oxygen species take part in the inflammatory response to carrageenan [2, 25]. These reports are mostly from cell studies at concentrations that may not be reached in tissues.

Pain is part of the picture. The paw is not only swollen after carrageenan but also hyperalgesic, and many studies measure withdrawal thresholds as well as volume. [10]-Gingerol and related pungent compounds act on transient receptor potential vanilloid 1 channels on sensory neurons, which could contribute to analgesia through desensitisation, as with capsaicin [3, 24]. This raises a point of interpretation: some of the benefit seen in behavioural tests may come from effects on nociception and not on inflammation itself, and the two can be separated only by measuring both swelling and mediators in the tissue.

A mechanism that is rarely examined is nitric oxide. Because nitric oxide synthase (NOS) inhibitors reduce carrageenan oedema, a ginger extract might also act there [10, 11, 12]. A few studies report lower nitrite levels or reduced inducible nitric oxide synthase expression with ginger fractions, but the link to paw swelling in vivo has seldom been tested directly. Likewise the possible role of transient receptor potential channels, which gingerols are known to activate, in the pain and neurogenic components of the model remains largely speculative [3].

Evidence for antioxidant contributions is perhaps the easiest to generate and the hardest to interpret. Ginger extracts scavenge radicals in simple chemical tests such as the DPPH (2,2-diphenyl-1-picrylhydrazyl) radical assay and raise activities of superoxide dismutase and catalase in treated animals in some reports [2, 25]. Reactive oxygen species do form in the inflamed paw, but a free radical scavenging result in a test tube says little about activity in tissue, where concentrations,

compartments and competing reactions are very different. It is reasonable to regard antioxidant effects as supportive rather than as the principal explanation, until experiments show that blocking them removes the benefit.

6. SAFETY, CLINICAL CONTEXT AND GAPS

Ginger has a favourable safety record at dietary and moderate supplement doses, with heartburn, mild gastrointestinal upset and occasional diarrhoea the commonest complaints. Systematic reviews of its use for nausea reported few serious adverse events [1, 33]. Theoretical concerns include inhibition of platelet aggregation and interaction with anticoagulants, though clinical evidence of harm is limited, and pharmacological doses in animals are not an indication of what is safe in people [1, 6]. Toxicity studies of concentrated extracts are less complete than those of the whole spice.

Clinical evidence for pain and inflammatory conditions is mixed and moderate in size. A randomised trial of a ginger extract in knee osteoarthritis reported a modest improvement in pain, and a meta-analysis of osteoarthritis trials found a small to moderate benefit with considerable heterogeneity between trials [7, 30]. Systematic reviews of ginger for pain in general are cautious, and a study of exercise-induced muscle pain showed a small effect [31, 32]. The animal work therefore fits a picture of a mild anti-inflammatory and analgesic action, and not a replacement for established drugs.

Special populations and interactions deserve a line. Ginger is widely used by pregnant women for nausea, and the evidence base for that use suggests few problems at usual doses, though high-dose products have not been studied thoroughly [1, 33]. People who take warfarin, antiplatelet drugs or antidiabetic medicines are often advised to be careful with large amounts of ginger, because of its effects on platelet function and on glucose handling in animal studies. These cautions rest on limited evidence, and they should be proportionate. They still argue against assuming that a natural product needs no medicines review.

The main weaknesses of the preclinical literature are easy to list. Preparations are poorly characterised, group sizes are small, randomisation and blinding are seldom reported, and a single time point or dose is often used. Positive controls are sometimes given at doses that make comparison unfair, and vehicle effects are overlooked [14, 16]. Dose-response data, time-course curves and information about gingerol content should be standard, and the animal ethics framework should be described in the methods in line with the 3Rs. Future studies could improve matters by using chemically defined extracts, comparing against a standard drug at an effective dose, measuring mediators in paw tissue alongside swelling, and testing in at least one chronic model to see whether acute activity carries over [19, 20, 23]. Pharmacokinetic work in the same species would clarify exposure. Independent replication of promising results by laboratories with no stake in the product is probably the single most valuable step.

Translation from rodent to person is the largest gap. Ginger constituents are poorly water soluble and extensively conjugated, so plasma concentrations after ordinary oral doses are low, and formulations aimed at better absorption, such as lipid-based or nanoparticulate systems, are only beginning to be studied [3, 6]. A clinical trial would need a standardised extract, a defined dose and a validated pain or inflammation end point. The paw oedema work cannot supply any of these, but it can help to select candidate fractions for such trials, which is a respectable role for a screening model.

7. CONCLUSION

The literature supports a cautious statement. Ginger rhizome extracts, and the gingerols and shogaols they contain, reduce carrageenan-induced paw swelling in rodents, usually most clearly in the later, prostaglandin-dependent phase, and cell studies point to inhibition of cyclooxygenase-2 and of pro-inflammatory cytokine production as plausible mechanisms [21, 24, 26, 27, 28]. Results from other models and from human trials of osteoarthritis pain are broadly consistent with a mild effect [7, 30]. The agreement across

models is encouraging, though it does not make any single extract proven.

Confidence is held back by uneven methods. Extracts are seldom standardised, doses in animals exceed those reached by consumers, and key details of design are often missing [14, 16, 17]. Better work would characterise the preparation chemically, measure mediators as well as swelling, and report time courses, doses and blinding in full. Until then, the paw oedema findings are best read as support for further study, and not as evidence that ginger can stand in for conventional anti-inflammatory drugs. A well-characterised extract tested with full reporting would settle much of what remains uncertain.

8. ABBREVIATIONS

COX-2-Cyclooxygenase-2, DPPH-2,2-Diphenyl-1-picrylhydrazyl, HPLC-High-performance liquid chromatography, IL-1β-Interleukin 1 beta, NF-κB-Nuclear factor kappa B, NOS-Nitric oxide synthase, NSAID-Non-steroidal anti-inflammatory drug, PGE_2-Prostaglandin E_2, TNF-α-Tumour necrosis factor alpha

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10. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

11. CONFLICT OF INTERESTS

Declared none

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