N-Acetil-Glucosamina (NAG)

Glucosamina e NAG inibiscono la produzione di NO indotta da IL-1b nei condrociti, ma NAG inibisce anche la produzione di COX-2 e IL-6

The Journal of Immunology, 2001,166:5155–5160.

N-AcetylglucosaminePreventsIL-1β-Mediated Activation of Human Chondrocytes1

AlexanderR.Shikhman,†KlausKuhn,†NadaAlaaeddine,†andMartinLotz2†*

Abstract

Glucosamine represents one of the most commonly used drugs to treat osteoarthritis. However, mechanisms of its antiarthritic activities are still poorly understood. The present study identifies a novel mechanism of glucosamine-mediatedanti-inflammatory activity. It is shown that both glucosamine and N-acetylglucosamine inhibit IL-1β- and TNF-α-induced NO production in normal human articular chondrocytes. The effect of the sugars on NO production is specific, since several other monosaccharides, including glucose, glucuronic acid, and N-acetylmannosamine, do not express this activity. Furthermore, N-acetylglucosamine poly-mers, including the dimer and the trimer, also do not affect NO production. The observed suppression of IL-1β-induced NO production is associated with inhibition of inducible NO synthase mRNA and protein expression. Inaddition,N-acetylglucosamine also suppresses the production of IL-1β-induced cyclooxygenase-2 and IL-6. The constitutively expressed cyclooxygenase-1, how-ever, was not affected by the sugar. N-acetylglucosamine-mediated inhibition of the IL-1β response of human chondrocytes was not associated with the decreased inhibition of the mitogen-activated protein kinases c-JunN-terminalkinase, extracellular signal-relatedkinase, and p38, nor with activation of the transcription factor NF-kB. Inconclusion, these results demonstrate that N-acetylglucosamine expresses a unique range of activities and identifies a novel mechanism for the inhibition of inflammatory processes.

NAG stimola la proliferazione di tessuto cartilagineo, circondato da condroblasti

Enhanced healing of cartilaginous injuries by N-acetyl-d-glucosamine and glucuronic acid

Yasunori Tamaia, Katsuyuki Miyatakea, Yoshiharu Okamotoa, Yoshimori Takamorib, Koji Sakamotob, Saburo Minamia,

Abstract

We investigated the restorative effect of orally administered glucose, N-acetyl-d-glucosamine (GlcNAc) and glucuronic acid (GlcUA) on the experimentally produced cartilaginous injuries in rabbits. A total of three holes in the left stifle joint, including one in the medial trochlear ridge, and two in the trochlear sulcus (proximal and distal) of articular cartilage were made surgically using a

drill. For the control group, only tap water was administered daily and for the glucose, GlcNAc, GlcUA groups, a water based solution (1 g/head/day) of glucose, GlcNAc, glucuronolactone was administered daily, respectively. We observed the clinical symptoms daily and the condition of the injured part was observed macroscopically and histologically at 3 weeks after the operation. There was no difference in body weight or general conditions among each group. With respect to medial trochlear injury, 1/3 holes were not cured in the control, but all were cured in the glucose, GlcNAc and GlcUA groups, respectively. With respect to the proximal hole, 4/6 in the control group, 3/3 in the glucose and 2/3 in the GlcNAc were not cured. However, 2/3 in the GlcUA were cured. There was significant difference ($p<0.05$) in the proximal holes between the control and the GlcUA. On the total points, there was significant difference ($p<0.05$) between the control and GlcNAc or GlcUA.

On histological examination, the injured parts were covered by fibrous connective tissues in the control and the glucose, whereas in the GlcNAc and GlcUA groups, the massive proliferation of matured cartilaginous tissues was observed, and the regenerated cartilaginous tissues were surrounded by the proliferation of chondroblast cells. In the regenerated tissue, matured cartilage substrate was also observed. Safranin O and Alcian blue stains marked a more significantly dense in the GlcNAc and GlcUA group than in the control ($p<0.01$) in injured parts as well as in non-injured joint cartilage.

Miglioramento dei sintomi da OA dopo somministrazione di latte di soia con NAG (1g/ die per 12 settimane)

Jpn Pharmacol.Ther 34;149 JANUARY 2006

Effects and safety of soymilk beverage containing N-acetyl glucosamine on osteoarthritis

K. Hatano Y. Miyakuni K. Hayashida S. Nakagawa –

Abstract

N-acetyl glucosamine is an amino sugar and a monomeric unit of chitin, a polysaccharide forming structural polymers in the exoskeletons of crustaceans. In humans, it exists in skin, cartilage and blood vessel as a component of hyaluronic acid, and bone tissue, cornea and aorta as a component of keratan sulfate. Osteoarthritis is one of the representative diseases, which disturb joint function and decrease the quality of life. One of the possible causes of osteoarthritis is decrease of amount of N-acetyl glucosamine in age, then feeding N-acetyl glucosamine could become its symptom better. In the present study, we assessed the effect and safety of a soymilk beverage containing N-acetyl glucosamine on osteoarthritis of knee joint, in the way of double-blind placebo-controlled, parallel group study. The subjects were 67 adults (male/female: 27/40, age: 54.3 ± 12.8), who felt slight pain, stiffness, and/or discomfort in their knee joints. They had never been treated the knee osteoarthritis by medication. The treatment group was given, once a day for 12 weeks, the test beverage (200mL) containing 1000 mg or more of N-acetyl glucosamine, and the control group was given the soymilk beverage without N-acetyl glucosamine. The results revealed that, the pain on going up and down the stairs and the pain at rest were significantly reduced in the treatment group compared with the placebo group at 8 week. Range of motion (ROM) in the treatment group was also significantly improved compared with the placebo group at 8 week. Blood examination, physical examination and history taking did not reveal any adverse reactions of clinical importance. These results thus demonstrated that the long-term intake of the soymilk beverage containing N-acetyl glucosamine improves the subjective symptom and range of motion in subjects with slight pain, stiffness, and/or discomfort at knee joint.

Glucosamina e insulino-resistenza

Diabetes. 1999 May;48(5):1101-7.

Allosteric regulation of glycogen synthase and hexokinase by glucosamine-6-phosphate during glucosamine-induced insulin resistance in skeletal muscle and heart.

Virkamäki A1, Yki-Järvinen H.

Abstract

Glucosamine infusion induces insulin resistance in vivo, but the effect of glucosamine on intracellular metabolites of the hexosamine pathway, especially glucosamine-6-phosphate (GlcN6P) is unknown. Because of the structural similarity of glucose-6-phosphate (G-6-P) and GlcN6P, we hypothesized that accumulation of this metabolite might alter the activities of enzymes such as glycogen synthase and hexokinase. We infused glucosamine (30 micromol x kg(-1) x min(-1)) to induce insulin resistance in rats during a euglycemic-hyperinsulinemic clamp. Glucosamine induced whole-body insulin resistance, which was apparent after 90 min and continued progressively for 360 min. Despite inducing severe whole-body insulin resistance and decrease in glycogen synthase fractional activity in rectus abdominis muscle (69+/-3 vs. 83+/-1%, P<0.01) and heart (7+/-1 vs. 32+/-4%, P<0.001), glucosamine did not change the glycogen content in rectus and even increased it in the heart (209+/-13 vs. 117+/-9 mmol/kg dry wt, P<0.001). Glucosamine increased tissue concentrations of UDP-GlcNAc 4.4- and 4.6-fold in rectus abdominis and heart, respectively. However, GlcN6P concentrations increased 500- and 700-fold in glucosamine-infused animals in rectus abdominis (590+/-80 vs. 1.2+/-0.1 micromol/kg wet wt, P<0.001) and heart (7,703+/-993 vs. 11.2+/-2.3 micromol/kg wet wt, P<0.001). To assess the possible significance of GlcN6P accumulation, we measured the effect of GlcN6P on glycogen synthase and hexokinase activity in vitro. At the GlcN6P concentrations measured in rectus abdominis and heart in vivo, glycogen synthase was activated by 21 and 542%, while similar concentrations inhibited hexokinase activity by 5 and 46%, respectively. This study demonstrates that infusion of glucosamine during a euglycemic-hyperinsulinemic clamp results in marked accumulation of intracellular GlcN6P. The GlcN6P concentrations in the heart and rectus abdominis muscle reach levels sufficient to cause allosteric activation of glycogen synthase and inhibition of hexokinase.

Endocrinology 140:1151–1157, 1999 DIABETES, VOL. 49, JUNE 2000

High Glucose and Glucosamine Induce Insulin Resistance via Different Mechanisms in 3T3-L1 Adipocytes

Bryce A. Nelson, Katherine A. Robinson, and Maria G. Buse

Abstract

Sustained hyperglycemia induces insulin resistance, but the mechanism is still incompletely understood. Glucosamine (GlcN) has been extensively used to model the role of the hexosamine synthesis pathway (HSP) in glucose-induced insulin resistance. 3T3-L1 adipocytes were preincubated for 18 h in media ± 0.6 nmol/l insulin containing either low glucose (5 mmol/l), low glucose plus GlcN (0.1–2.5 mmol/l), or high glucose (25 mmol/l). Basal and acute insulin-stimulated (100 nmol/l) glucose transport was measured after re-equilibration in serum and insulin-free media. Preincubation with high glucose or GlcN (1–2.5 mmol/l) inhibited basal and acute insulinstimulated glucose transport only if insulin was present during preincubation. However, only preincubation with GlcN plus insulin inhibited insulin-stimulated GLUT4 translocation. GLUT4 and

GLUT1 protein expression were not affected. GlcN (2.5 mmol/l) increased cellular UDP-N-acetylhexosamines (UDP-HexNAc) by 400 and 900% without or with insulin, respectively. High glucose plus insulin increased UDP-HexNAc by 30%. GlcN depleted UDP-hexoses, whereas high glucose plus insulin increased them. Preincubation with 0.5 mmol/l GlcN plus insulin maximally increased UDP-HexNAc without affecting insulin-stimulated or basal glucose transport. GlcN plus insulin (but not high glucose plus insulin) caused marked GlcN dose-dependent accumulation of GlcN-6-phosphate, which correlated with insulin resistance of glucose transport (r = 0.935). GlcN plus insulin (but not high glucose plus insulin) decreased ATP (10–30%) and UTP (>50%). GTP was not measured, but GDP increased. Neither high glucose plus insulin nor GlcN plus insulin prevented acute insulin stimulation (~20-fold) of insulin receptor substrate 1–associated phosphatidylinositol (PI)-3 kinase. We have come to the following conclusions. 1) Chronic exposure to high glucose or GlcN in the presence of low insulin caused insulin resistance of glucose transport by different mechanisms. 2) GlcN inhibited GLUT4 translocation, whereas high glucose impaired GLUT4 “intrinsic activity” or membrane intercalation. 3) Both agents may act distally to PI-3 kinase. 4) GlcN has metabolic effects not shared by high glucose. GlcN may not model HSP appropriately, at least in 3T3-L1 adipocytes.

NAG non induce insulino-resistenza

Metabolism May 1964Volume 13, Issue 5, Pages 466–472

The effect of intravenous N-acetyl-D-glucosamine on the blood and urine sugar concentrations of normal subjects

E.C. Gaulden, M.D. William C. Keating, M.D.

Abstract

Studies of several investigators have suggested that N-Acetylglucosamine may be useful as a sugar substitute feeding in postoperative subjects and patients with diabetes and liver disease. It is incorporated into body tissues, including the liver where it forms glycogen,1 but its removal from the blood is not significantly affected by insulin.3 It is, at the same time, a source of oral and parenteral nitrogen which does not seem to increase blood ammonia as do some of the protein hydrolysates.8 Ten apparently healthy volunteers with normal glucose tolerance test results were chosen as subjects. Following intravenous administration, N-Acetyl-D-Glucosamine metabolism was compared with that of dextrose in a cross-over design by determining glucose and total reducing substances in the blood, and 24 hour excretion of reducing substances in the urine. It was found that intravenous administration of NADG produces little or no significant change in blood dextrose concentration as measured by the orthotoluidine method. The curve of blood dextrose concentrations differed from that obtained when total reducing substancse were determined. The curve of the concentrations of reducing substances in the blood following administration of NADG is parabolic with a gradual return to the baseline. This contrasts with the curve obtained after dextrose administration; the peak is rapidly attained within 1 hour followed by a precipitous drop to baseline or to below control levels. These data strongly suggest that NADG is metabolized into fragments after intravenous administration; however, virtually none is converted to dextrose. Removal of NADG from the blood represents the sum of the fates of this substance within the body. When 100 Gm. are administered intravenously within 1 hour, approximately 30 per cent are excreted in the urine. Some may be excreted in the gut and the remainder are metabolized in the body. Further studies may indicate that NADG is a suitable sugar substitute for diabetics and a useful nutritional supplement for postoperative subjects and patients with liver disease.

ZENZERO

Effetto anti-infiammatorio dello Zenzero su cellule sinoviali isolate di membrana sinoviale o liquido sinoviale stimolato da TNF-alfa: le cellule trattate con Zenzero hanno mostrato un effetto inibitorio comparabile a quello ottenuto con betametasone inibendo la produzione di citochine IL-1 e IL-6

Arthritis. 2012;2012:505842. doi: 10.1155/2012/505842. Epub 2012 Dec 31.

A synoviocyte model for osteoarthritis and rheumatoid arthritis: response to Ibuprofen, betamethasone, and ginger extract-a cross-sectional in vitro study.

Ribel-Madsen S1, Bartels EM, Stockmarr A, Borgwardt A, Cornett C, Danneskiold-Samsøe B, Bliddal H.

Abstract

This study aimed at determining if synovial cell cultures from rheumatoid arthritis (RA), osteoarthritis (OA), and healthy controls (HC) differ and are suitable disease models in pharmacological studies, and tested their response to some anti-inflammatory drugs. Synovial cells were isolated from synovial membrane or joint fluid. Cells were cultivated and exposed to no or TNF-α stimulation without, or in the presence of, betamethasone, ibuprofen, or a standardized ginger extract. Concentrations of a panel of cytokines, growth factors, and chemokines were mapped for each culture and condition. Our cells secreted an increased amount of the cytokines IL-1β, IL-6, and IL-8 in response to TNF-α stimulation in all conditions. OA cells showed a higher IL-6 and IL-8 and a lower IL-1β production, when not stimulated, than RA and HC cells, which were similar. TNF-α stimulation caused similar IL-1β, IL-6, and IL-8 release in all groups. Ibuprofen showed no effect on cytokine production, while ginger extract was similar to betamethasone. Ginger extract was as effective an anti-inflammatory agent as betamethasone in this in vitro model. Cultured fibroblast-like synoviocytes from OA and RA subjects promise to be a useful pharmacological disease model, but further studies, to support results from such a model are needed.

Gingerolo e gingerdione hanno manifestato in modo significativo attività analgesica e antiinfiammatoria inibendo la sintesi di PGE2

Prostaglandins Leukot Med. 1986 Oct;24(2-3):195-8.

Inhibition of human neutrophil 5-lipoxygenase activity by gingerdione, shogaol, capsaicin and related pungent compounds.

Flynn DL, Rafferty MF, Boctor AM.

Abstract

A series of structurally related pungent natural products including capsaicin, gingerol, and gingerdione among others were evaluated and found to be potent inhibitors of 5-HETE biosynthesis in intact human leukocytes, with IC50 values of 100 and 15 microM for capsaicin and gingerdione, respectively. Several compounds within this series were also found to inhibit PGE2 formation, with the most potent being gingerdione (IC50 = 18 microM). These and other data indicate that members of the capsaicin/gingerol family of pungent compounds can act as dual inhibitors of arachidonic acid metabolism, which could account in part for the antiinflammatory and analgesic properties of compounds within this group.

10-gingerolo, l'8-shogaol, e il 10-shogaol inibiscono l'enzima COX 2 riducendo significativamente l'infiammazione.

Fitoterapia. 2011 Jan;82(1):38-43. doi: 10.1016/j.fitote.2010.09.004. Epub 2010 Sep 15.

Cyclooxygenase-2 inhibitors in ginger (Zingiber officinale).

van Breemen RB1, Tao Y, Li W.

Abstract

Ginger roots have been used to treat inflammation and have been reported to inhibit cyclooxygenase (COX). Ultrafiltration liquid chromatography mass spectrometry was used to screen a chloroform partition of a methanol extract of ginger roots for COX-2 ligands, and 10-gingerol, 12-gingerol, 8-shogaol, 10-shogaol, 6-gingerdione, 8-gingerdione, 10-gingerdione, 6-dehydro-10-gingerol, 6-paradol, and 8-paradol bound to the enzyme active site. Purified 10-gingerol, 8-shogaol and 10-shogaol inhibited COX-2 with IC(50) values of 32 μM, 17.5 μM and 7.5 μM, respectively. No inhibition of COX-1 was detected. Therefore, 10-gingerol, 8-shogaol and 10-shogaol inhibit COX-2 but not COX-1, which can explain, in part, the anti-inflammatory properties of ginger.

Attività inibitoria del gingerolo sui canali TRP

Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease - Volume 1772, Issue 8, August 2007, Pages 978–988

TRP channels and pain

Daniel N. Cortright, ,James E. Krause, Daniel C. Broom

Abstract

Since the molecular identification of the capsaicin receptor, now known as TRPV1, transient receptor potential (TRP) channels have occupied an important place in the understanding of sensory nerve function in the context of pain. Several TRP channels exhibit sensitivity to substances previously known to cause pain or pain-like sensations; these include cinnamaldehyde, menthol, gingerol, and icillin. Many TRP channels also exhibit significant sensitivity to increases or decreases in temperature. Some TRP channels are sensitized in vitro by the activation of other receptors such that these channels may be activated by processes, such as inflammation that result in pain. TRP channels are suggested to be involved in processes as diverse as sensory neuron activation events, neurotransmitter release and action in the spinal cord, and release of

inflammatory mediators. These functions strongly suggest that specific and selective inhibition of TRP channel activity will be of use in alleviating pain.

Parità di efficacia con diclofenac nel trattamento dell'OA, ma con un profilo di tollerabilità superiore

J Altern Complement Med. 2012 Jun;18(6):583-8. doi: 10.1089/acm.2011.0202.

Influence of a specific ginger combination on gastropathy conditions in patients with osteoarthritis of the knee or hip.

Vladimir N. Drozdov, MD, Victoria A. Kim, PhD, Elena V. Tkachenko, MD, and Galina G. Varvanina, MD

Health Care Department, The Central Gastroenterology Scientific Research Institute, Moscow, Russia.

Abstract

Background: Nonsteroid anti-inflammatory drugs represent an important osteoarthritis (OA) therapy component, but also a leading cause of gastropathy: one of the most frequent and serious OA therapy complications. The aim of the present study was to study the influence of GI health in an OA population receiving either ginger or diclofenac.

Methods: Forty-three (43) patients with confirmed OA (knee and hip) were included in a randomized controlled study. A ginger group of 21 patients (17 women, 4 men) was given a specific ginger combination daily (340 mg EV.EXT 35 Zingiber officinalis extract) for 4 weeks. A diclofenac group (positive control) of 22 patients (18 women, 4 men) received 100 mg diclofenac daily for the same period. Both groups also received 1000 mg glucosamine daily. Gastrointestinal pain and dyspepsia were evaluated according to the severity of dyspepsia assessment (SODA) form. Patients also underwent esophagogastroduodenoscopy (EGDS) including biopsy before and after the treatment. Serum gastrin-17 levels, and stomach mucosa prostaglandins (PG) E1, E2, F2α, and 6-keto PGF1α (PGI2) levels were measured. Arthritic pain was evaluated using the visual analogue scale (VAS) on standing and moving.

Results: The ginger group showed a slight but significantly lowered SODA pain and no change of SODA dyspepsia. EGDS showed significantly increased levels of PGE1, PGE2, and PGF2α in the stomach mucosa. This rise in gastric mucosa PG levels correlated with an increase in serum gastrin-17. On the other hand, the diclofenac group showed increased SODA pain and dyspepsia values with a corresponding significant decrease of stomach mucosa prostaglandins and general negative stomach mucosa degeneration. Both groups showed a relevant and significantly lowered VAS pain both on standing and moving.

Conclusions: The ginger combination is as effective as diclofenac but safer in treating OA, being without effect on the stomach mucosa. The increased mucosal PGs synthesis in the ginger group supports an increased mucosa-protective potential.

Efficacia dell'estratto di zenzero nella riduzione dei sintomi da OA al ginocchio

Arthritis Rheum. 2001 Nov;44(11):2531-8.

Effects of a ginger extract on knee pain in patients with osteoarthritis.

Altman RD1, Marcussen KC.

Abstract

OBJECTIVE:

To evaluate the efficacy and safety of a standardized and highly concentrated extract of 2 ginger species, Zingiber officinale and Alpinia galanga (EV.EXT 77), in patients with osteoarthritis (OA) of the knee.

METHODS:

Two hundred sixty-one patients with OA of the knee and moderate-to-severe pain were enrolled in a randomized, double-blind, placebo-controlled, multicenter, parallel-group, 6-week study. After washout, patients received ginger extract or placebo twice daily, with acetaminophen allowed as rescue medication. The primary efficacy variable was the proportion of responders experiencing a reduction in "knee pain on standing," using an intent-to-treat analysis. A responder was defined by a reduction in pain of > or = 15 mm on a visual analog scale.

RESULTS:

In the 247 evaluable patients, the percentage of responders experiencing a reduction in knee pain on standing was superior in the ginger extract group compared with the control group (63% versus 50%; P = 0.048). Analysis of the secondary efficacy variables revealed a consistently greater response in the ginger extract group compared with the control group, when analyzing mean values: reduction in knee pain on standing (24.5 mm versus 16.4 mm; P = 0.005), reduction in knee pain after walking 50 feet (15.1 mm versus 8.7 mm; P = 0.016), and reduction in the Western Ontario and McMaster Universities osteoarthritis composite index (12.9 mm versus 9.0 mm; P = 0.087). Change in global status and reduction in intake of rescue medication were numerically greater in the ginger extract group. Change in quality of life was equal in the 2 groups. Patients receiving ginger extract experienced more gastrointestinal (GI) adverse events than did the placebo group (59 patients versus 21 patients). GI adverse events were mostly mild.

CONCLUSION:

A highly purified and standardized ginger extract had a statistically significant effect on reducing symptoms of OA of the knee. This effect was moderate. There was a good safety profile, with mostly mild GI adverse events in the ginger extract group.

L'estratto di zenzero migliora l'efficacia del diclofenac in pazienti con l'OA del ginocchio

Indian J Physiol Pharmacol. 2013 Apr-Jun;57(2):177-83.

Efficacy and tolerability of ginger (Zingiber officinale) in patients of osteoarthritis of knee. Paramdeep G.

Abstract

Osteoarthritis (OA) is a chronic degenerative disorder of synovial joints and a common cause of locomotor disability. NSAIDs are routinely used for symptomatic treatment and are associated with side effects which have led to the increased interest towards alternative treatment options. This study was conducted to evaluate the safety and efficacy of ginger in management of OA. Sixty patients of OA of knee were enrolled in randomized open label study and divided into three groups of 20 each. Group I received tab. Diclofenac 50 mg and cap. placebo, group II received cap. ginger 750 mg and cap. placebo and group III received cap. ginger 750 mg and tab. diclofenac 50 mg. The assessment of efficacy was done at every 2 weeks till 12 weeks, by using Western Ontario and McMaster Universities osteoarthritis (WOMAC) index, Visual Analogue Scale (VAS) and the safety assessment was done by noting adverse events during the study. The analysis of WOMAC score and VAS score in all the three groups showed statistically significant improvement with time in all groups. On comparison among three groups, group III patients who received both ginger and diclofenac showed numerically superior improvement than the individual treatments. There was no statistically significant difference among three groups in case of adverse events. Ginger powder has add-on effect on reducing the symptoms of OA of knee with acceptable safety profile.

Efficacia paragonabile di Ibuprofene e Zenzero sui sintomi dell'OA

Archives of Iranian medicine 08/2005; 8(4).

Comparing the Effects of ginger (Zingiber officinale) extract and ibuprofen on patients with osteoarthritis

Masoud Haghighi, Ali Khalvat, Tayebeh Toliat, Shohreh Jallaei

Abstract

Background: Ginger (Zingiber officinale) extract supplementation has been shown to improve the severity of symptoms and decrease the nonsteroidal antiinflammatory drug (NSAID) requirements in patients with osteoarthritis (OA). Objective: To assess the effects of ginger extract as an alternative to NSAIDs and as a supplement drug in the symptomatic treatment of OA. Methods: Between April and October 2002, 120 outpatients with OA of moderate to severe pain, requiring only the use of NSAIDs, were enrolled into a double-blind, randomized, placebo- controlled clinical trial. These patients were randomized into three groups of 40, including the placebo (PL), ginger extract (GE), and ibuprofen (IBP) groups. After a washout period of one week (week 0), patients received either 30 mg ginger extract in two 500 mg capsules, placebo, or three 400 mg ibuprofen tablets daily for one month. Acetaminophen tablet was prescribed as a rescue analgesic during the study. The clinical assessments included a visual analog scale (VAS) for pain, gelling pain, joint swelling measurement, and joint motion slope measurement. Joint motion slope was measured by goniometry (normal = 130°, limited = 120°, and very limited = 110°). Results: The improvement of symptoms (defined as reduction in the mean change) was superior in the ginger extract and ibuprofen groups than the placebo group. VAS scores and gelling or regressive pain after rising the scores were significantly higher in the PL group than both the GE and IBP groups, a month after the treatment ($P < 0.0001$). However, there was no significant difference in VAS and gelling pain scores between the ginger extract and the ibuprofen groups. Conclusion: Ginger extract and ibuprofen were significantly more effective than the placebo in the symptomatic treatment of OA, while there was no significant difference between the ginger extract and ibuprofen groups in a test for multiple comparison.

BOSWELLIA SERRATA

L'azione inibitrice sull'espressione delle metallo proteasi come meccanismo antinfiammatorio

Antioxidants & Redox Signaling

Regulation of Vascular Responses to Inflammation: Inducible Matrix Metalloproteinase-3 Expression in Human Microvascular Endothelial Cells Is Sensitive to Antiinflammatory Boswellia

Dr. Sashwati Roy - Laboratory of Molecular Medicine, Department of Surgery, The Ohio State University Medical Center, Columbus, OH.

Abstract

Endothelial cells are critical elements in the pathophysiology of inflammation. Tumor necrosis factor (TNF) α potently induces inflammatory responses in endothelial cells. Recently we have examined the genetic basis of the antiinflammatory effects of Boswellia extract (BE) in a system of TNFα-induced gene expression in human microvascular endothelial cells (HMECs). Of the 522 genes induced by TNFα in HMECs, 113 genes were sensitive to BE. BE prevented the TNFα-induced expression of matrix metalloproteinases (MMPs). In the current work, we sought to test the effects of BE on TNFα-inducible MMP expression in HMECs. Acetyl-11-ketobeta- boswellic acid (AKBA) is known to be an active principle in BE. To evaluate the significance of AKBA in the antiinflammatory properties of BE, effects of BE containing either 3% (BE3%) or 30% (BE30%, 5-Loxin®) were compared. Pretreatment of HMECs for 2 days with BE potently prevented TNFα-induced expression and activity of MMP-3, MMP-10, and MMP-12. In vivo, BE protected against experimental arthritis. In all experiments, both in vitro and in vivo, BE30% was more effective than BE3%. In sum, this work lends support to our previous report that BE has potent antiinflammatory properties both in vitro as well as in vivo.

Identificazione dei target che spiegano l'effetto antinfiammatorio della Boswellia, tra cui le 5-lipossigenasi e le elastasi

Current Medicinal Chemistry, Volume 13, Number 28, December 2006

Boswellic Acids: Biological Actions and Molecular Targets

Authors: Poeckel, Daniel; Werz, Oliver

Abstract

Gum resin extracts of Boswellia species have been traditionally applied in folk medicine forcenturies to treat various chronic inflammatory diseases, and experimental data from animal models andstudies with human subjects confirmed the potential of B. spec extracts for the treatment of not onlyinflammation but also of cancer. Analysis of the ingredients of these extracts

revealed that the pentacyclictriterpenes boswellic acids (BAs) possess biological activities and appear to be responsible for the respective pharmacological actions. Approaches in order to elucidate the molecular mechanisms underlying thebiological effects of BAs identified 5-lipoxygenase, human leukocyte elastase, toposiomerase I and II, as wellas IκB kinases as molecular targets of BAs. Moreover, it was shown that depending on the cell type and the structure of the BAs, the compounds differentially interfere with signal transduction pathways including Ca2+-and MAPK signaling in various blood cells, related to functional cellular processes important for inflammatory reactions and tumor growth. This review summarizes the biological actions of BAs on the cellular and molecular level and attempts to put the data into perspective of the beneficial effects manifested in animal studies and trials with human subjects related to inflammation and cancer.

Inibizione di 5-lipossigenasi, citochine ed elastasi alla base dell'attività antinfiammatoria dell'estratto di Boswellia

Planta Med. 2006 Oct;72(12):1100-16.

Boswellic acids in chronic inflammatory diseases.

Ammon HP1.

Abstract

Oleogum resins from BOSWELLIA species are used in traditional medicine in India and African countries for the treatment of a variety of diseases. Animal experiments showed anti-inflammatory activity of the extract. The mechanism of this action is due to some boswellic acids. It is different from that of NSAID and is related to components of the immune system. The most evident action is the inhibition of 5-lipoxygenase. However, other factors such as cytokines (interleukins and TNF-alpha) and the complement system are also candidates. Moreover, leukocyte elastase and oxygen radicals are targets. Clinical studies, so far with pilot character, suggest efficacy in some autoimmune diseases including rheumatoid arthritis, Crohn's disease, ulcerative colitis and bronchial asthma. Side effects are not severe when compared to modern drugs used for the treatment of these diseases.

Efficacia significativa dell'estratto di B. in confronto con placebo, su parametri del dolore ed infiammazione nell'OA del ginocchio (8 settimane)

Phytomedicine. 2003 Jan;10(1):3-7.

Efficacy and tolerability of Boswellia serrata extract in treatment of osteoarthritis of knee--a randomized double blind placebo controlled trial.

Kimmatkar N1, Thawani V, Hingorani L, Khiyani R.

Abstract

Osteoarthritis is a common, chronic, progressive, skeletal, degenerative disorder, which commonly affects the knee joint. Boswellia serrata tree is commonly found in India. The therapeutic value of its gum (guggulu) has been known. It posses good anti-inflammatory, anti-arthritic and analgesic activity. A randomized double blind placebo controlled crossover study was conducted to assess

the efficacy, safety and tolerability of Boswellia serrata Extract (BSE) in 30 patients of osteoarthritis of knee, 15 each receiving active drug or placebo for eight weeks. After the first intervention, washout was given and then the groups were crossed over to receive the opposite intervention for eight weeks. All patients receiving drug treatment reported decrease in knee pain, increased knee flexion and increased walking distance. The frequency of swelling in the knee joint was decreased. Radiologically there was no change. The observed differences between drug treated and placebo being statistically significant, are clinically relevant. BSE was well tolerated by the subjects except for minor gastrointestinal ADRs. BSE is recommended in the patients of osteoarthritis of the knee with possible therapeutic use in other arthritis.

Confronto con un coxib nell'OA del ginocchio (6 mesi); l'estratto di Boswellia agisce più lentamente del coxib, ma l'efficacia si protrae a lungo dopo la cessazione del trattamento

Indian Journal of Pharmacology 2007

Open, randomized, controlled clinical trial of Boswellia serrata extract as compared to valdecoxib in osteoarthritis of knee

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Objective: To compare the efficacy, safety and tolerability of Boswellia serrata extract (BSE) in osteoarthritis (OA) knee with valdecoxib, a selective COX-2 inhibitor. Materials and Methods: In a randomized, prospective, open-label, comparative study the efficacy, safety and tolerability of BSE was compared with valdecoxib in 66 patients of OA of knee for six months. The patients were assessed by WOMAC scale at baseline and thereafter at monthly interval till 1 month after drug discontinuation. Antero-posterior radiographs of affected knee joint were taken at baseline and after 6 months. Results: In BSE group the pain, stiffness, difficulty in performing daily activities showed statistically significant improvement with two months of therapy which even lasted till one month after stopping the intervention. In valdecoxib group the statistically significant improvement in all parameters was reported after one month of therapy but the effect persisted only as long as drug therapy continued. Three patients from BSE group and two from valdecoxib group complained of acidity. One patient from BSE group complained of diarrhea and abdominal cramps. Conclusion: BSE showed a slower onset of action but the effect persisted even after stopping therapy while the action of valdecoxib became evident faster but waned rapidly after stopping the treatment.

CENTELLA

In Vitro and *In Vivo* Modulation of Cartilage Degradation by a Standardized *Centella asiatica* Fraction

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Abstract

Osteoarthritis (OA) is a degenerative joint disease in which focal cartilage destruction is one of the primary features. The present study aims to evaluate the effect of a *Centella asiatica* fraction on *in vitro* and *in vivo*cartilage degradation. Bovine cartilage explants and bovine chondrocytes cultured in alginate were stimulated with IL-1β in the presence or absence of different concentrations (2, 5 and 10 μg/ml) of a standardized *Centella asiatica* triterpenes (CAT) fraction. The CAT fraction inhibited the IL-1β-induced proteoglycan (PG) release and nitric oxide (NO) production by cartilage explants in a dose-dependent manner. The IL-1β-induced reduction in PG synthesis and proliferation of chondrocytes cultured in alginate were counteracted by the CAT fraction at a concentration of 10 μg/ml. In a zymosan-induced acute arthritis model, the CAT fraction inhibited PG depletion without modulating joint swelling and inflammatory cell infiltration. In conclusion, the present study demonstrated for the first time that the tested *Centella asiatica* fraction was able to inhibit the zymosan-induced cartilage degradation *in vivo* without affecting the zymosan-induced inflammatory cell infiltration and joint swelling. The *in vitro* data indicate that the cartilage protective activity might at least partially be induced by the inhibition of NO production. The overall results indicate a possible disease modifying osteoarthritic activity of the *Centella asiatica* fraction.

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Triterpenes from Centella asiatica stimulate extracellular matrix accumulation in rat experimental wounds.

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Abstract
Titrated Extract from Centella asiatica (TECA) is a drug which has been used for many years in Europe for the treatment of wound healing defects. It is a reconstituted mixture of 3 triterpenes extracted from the plant, asiatic acid, madecassic acid and asiaticoside. In this report, we studied the effects of TECA and its separated components in the wound chamber model described by Schilling et al. Stainless steel wound chambers were surgically inserted under the skin of rats and received serial injections of either TECA or its purified components. Chambers were collected at days 7, 14, 21 or 28 for biochemical analysis or histological examination. TECA-injected wound chambers were characterized by increased dry weight, DNA, total protein, collagen and uronic acid contents. Peptidic hydroproline was also increased, showing an increased remodeling of the collagen matrix in the wound. The 3 purified components of TECA were all able to reproduce the effects of the complete drug, with some differences depending on the product. Asiatic acid and asiaticoside were the most active of the 3 triterpenes. Asiaticoside exerted a preferential stimulation of collagen synthesis and was active at low doses only. In addition to collagen, the 3 components were also able to stimulate glycosaminoglycan synthesis.

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Review

The Effect of Ginger and Its Sub-Components on Pain

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Abstract: *Zingiber officinale* Roscoe (ginger) has long been used as an herbal medicine to treat various diseases, and its main sub-components, [6]-gingerol and [6]-shogaol, were also reported to have anti-inflammatory, anti-oxidant, and anti-tumor effects. However, their effects on various types of pain and their underlying mechanisms of action have not been clearly analyzed and understood yet. Thus, in this review, by analyzing 16 studies that used *Z. officinale*, [6]-gingerol, and [6]-shogaol on mechanical, spontaneous and thermal pain, their effects and mechanisms of action have been analyzed. Pain was induced by either nerve injury or chemical injections in rodents. Nine studies analyzed the analgesic effect of *Z. officinale*, and four and three studies focused on [6]-gingerol and [6]-shogaol, respectively. Seven papers have demonstrated the underlying mechanism of action of their analgesic effects. Studies have focused on the spinal cord and one on the dorsal root ganglion (DRG) neurons. Involvement and change in the function of serotonergic receptors (5-$HT_{1A, B, D,}$ and $_{5A}$), transient receptor potential vanilloid 1 (TRPV1), N-methyl-D-aspartate (NMDA) receptors, phosphorylated extracellular signal-regulated kinase 1/2 (pERK1/2), histone deacetylase 1 (HDAC1), voltage-gated sodium channel 1.8 ($Na_v1.8$), substance P (SP), and sciatic nerve's morphology have been observed.

Keywords: [6]-gingerol; [6]-shogaol; ginger; pain; *Zingiber officinale* Roscoe

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1. Introduction

Zingiber officinale Roscoe is a perennial herb from a member of the Zingiberaceae family [1], and it is known to be rich in various chemical constituents, such as phenolic compounds, terpenes, polysaccharides, lipids, organic acids, and raw fibers [2]. Among the main phenolic compound, gingerols, which are a mixture containing the 3-methoxy-4-hydroxyphenyl functional group, induce *Z. officinale*'s spicy taste and are present in 85 types [3]. Gingerols can be divided into gingerols, shogaols, paradols and zingerones. Among them, gingerols and shogaols are known as the most important physiological active ingredients for *Z. officinale*, of which [6]-gingerol and [6]-shogaol are the main compounds [4].

In the international association for the study of pain (IASP), pain is defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage." Additionally, pain extends its meaning to personal experiences affected by biological, psychological, and social factors [5]. Pain is present in various forms, such as acute and chronic [6], neuropathic [7], inflammatory [8], and cancer [9] pain. To manage these various types of pain, diverse analgesics are used. Among them, opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most widely used pain-reducing drugs in the world. In 2012, 6.8% of the 4.2 billion prescriptions prepared in the United States were opioids [10], and from 2001 to 2009, the number of people who prescribed NSAIDs more than doubled [11]; however, both opioids and NSAIDs have side

effects such as hormone imbalance [12], tolerance and dependence [13], nausea, dyspepsia and gastrointestinal ulceration [14]. Thus, efforts to find an optimal analgesic drug that has no or fewer side effects than the currently used analgesics are still needed.

Z. officinale, ginger, has long been widely used as an herbal medicine for the prevention and treatment of various diseases [15–17], as it has also been reported to show no toxic effects [18]. In clinical studies, it has been reported to alleviate diseases such as diabetes [19–21], obesity [22], cancer [23], nausea and vomiting [24]. Furthermore, although low in numbers, *Z. officinale* has also been demonstrated to be effective against different types of pain in humans. Its administration with NSAIDs have decreased migraine attack compared to the placebo-treated group [25]. A systematic review has reported the efficacy of *Z. officinale* to treat primary dysmenorrhea [26], and a clinical report has demonstrated that osteoarthritis patients receiving both *Z. officinale* extract and ibuprofen showed significantly reduced pain [27]. Although more than ten papers, which have focused on the effect of *Z. officinale* and its sub-components on pain have been published, to date no study has summarized the effect of *Z. officinale* and its sub-components on various types of pain.

From the past, our lab has focused our efforts to understand the pathophysiological and curative mechanism of different types of pain, such as chemotherapy-induced neuropathy (CIPN) [28,29] and diabetic-induced neuropathic pain [30]. In our previous study, the water extract of *Z. officinale* effectively attenuates chemotherapy-induced neuropathic pain [31], as cold and mechanical allodynia significantly decreased after the oral treatment of *Z. officinale* in mice. These data let us speculate that ginger and its sub-component could be used to treat different types of pain. Moreover, as it has been reported to not induce any lethal effects [18], if the understanding of the effect and the mechanism of action increases, it could be considered a good option to treat pain.

Thus, in this review, the effect of *Z. officinale*, [6]-gingerol, and [6]-shogaol has been summarized and analyzed along with the underlying mechanisms of action. This review study includes a total of 16 studies.

2. Results

This review includes a total of 16 studies (Tables 1 and 2). Nine studies analyzed the analgesic effect of *Z. officinale* [19,31–38], and four [39–42] and three [43–45] studies focused on [6]-gingerol and [6]-shogaol, respectively. To analyze their effects on different types of pain, studies have been subdivided into three types of pain; mechanical, spontaneous and thermal pain (Figure 1). The mechanical pain section contains seven studies, and the spontaneous and thermal pain section contains four and ten studies, respectively.

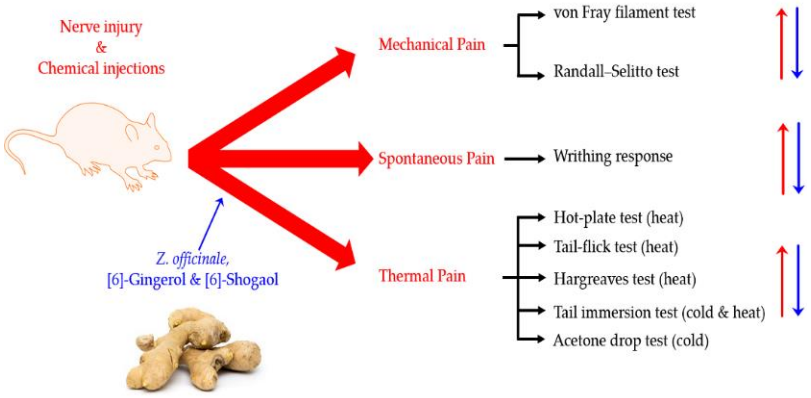

Figure 1. Analgesic effects of *Z. officinale*, [6]-gingerol and [6]-shogaol in mechanical, spontaneous, and thermal pain induced by nerve injury or chemical injection, and a summarization of behavior tests used in the experiment. The pain is induced by a nerve or chemical injection (Red) and alleviated by *Z. officinale* and its sub-components (Blue). Abbreviations: *Z. officinale* (*Zingiber officinale* Roscoe).

2.1. Mechanical Pain

Various sensory receptors are present on the skin, such as mechanoreceptors, thermoreceptors and nociceptors [46]. Among them, nociceptors transmit pain signals related to mechanical, thermal, or chemical [47]. Nociceptors include both myelinated and unmyelinated neurons such as Aβ-, Aδ- and C-fiber nociceptors, respectively. Among them, Aβ and Aδ nociceptor neurons are known to mediate mechanical sensation and pain [48]. Mechanical pain could be associated with nerve damage [49] and changed in the activities of various sodium channels (i.e., voltage-gated sodium channel (Na_v) 1.7 and Na_v1.8) [50]. In addition, the depression of gamma-Aminobutyric acid (GABA)ergic interneurons increases in the expression of transient receptor potential vanilloid 1 (TRPV1) [51], and the decrease in the potassium channel subfamily K member 1 (TREK-1) channel [52] has also been reported to be the cause of mechanical pain.

To assess the effect of *Z. officinale* and its sub-components on mechanical pain, studies used different types of nerve injury methods, such as chronic constraint injury (CCI) [40], spinal nerve ligation (SNL) [42], spared nerve injury (SNI) [38], and intermittent cold stress (ICS) [35], or chemicals such as acetic acid [41], streptozotocin (STZ) [43,44] and oxaliplatin [31] to induce pain in rodents. Mechanical pain has been evaluated by either von Frey filaments tests [31,38,40–42,44,45] or the Randall–Selitto test [35,43].

Nerve-injury-induced animal models of pain have been used by both Gauthier et al. [40], Mata-Bermudez et al. [42] and Borgonetti et al. [38]; however, the method was different, as Gauthier et al. used CCI, whereas Mata-Bermudez et al. and Borgonetti et al. used SNL and SNI animal models of pain, respectively. CCI consists of four loose ligations around the sciatic nerve damaging most of the myelinated neurons but leaving intact the unmyelinated C-fibers. The CCI-induced pain rodents demonstrate spontaneous, thermal, and mechanical pain, which appears from three days to two months after the injury [53]. SNL is the tight ligation of L5-6 spinal nerves. In this model, the degenerative fibers of the damaged roots come into contact with the distal portion of the undamaged roots [54]. In SNL models, L4 dorsal root ganglia (DRG) is unaffected, whereas L5-6 DRG is affected [55]. Pain occurs quickly after nerve ligation and lasts at least four months [56]. In SNI-induced pain, only the tibial and common peroneal nerves are axotomized, leaving the sural nerve intact. The undamaged fibers are in contact with the proximal part of the injured nerves [57]. SNI models differ from other surgery models in that they can examine distinct regions of the hind paw that are innervated by damaged or undamaged neurons. In addition, this model has been demonstrated to closely mimic many features of clinical neuropathic pain. SNI showed pain 24 h after surgery and reached its peak about two weeks later [58].

Nerve injury models such as CCI, SNL, SNI and partial sciatic nerve ligation (PSNL) models all measure the cutaneous sensory threshold of ipsilateral hind limb and these pains are evaluated mainly by thermal and mechanical stimuli [56,59].

Gauthier et al. [40] has reported that [6]-gingerol could effectively attenuate mechanical pain induced by CCI. The pain lasted from 1 to 10 days after the surgery, and intrathecally administered 10 μg of [6]-gingerol demonstrated an analgesic effect, which lasted till 4 h after the injection. In the study of Mata-Bermudez et al. [42], the same dose of [6]-gingerol also attenuated SNL-induced mechanical pain. The anti-analgesic effects of [6]-gingerol initiated 60 min after the administration, which gradually decreased after four hours. They further reported that various serotonin (5-HT) receptors, such as 5-$HT_{1A, 1B, 1D}$ and $_{5A}$, but not opioid receptors, are involved in the analgesic effect of [6]-shogaol. In addition, in their study, intrathecal pre-treatment of nonselective nitric oxide (NO) synthase inhibitor, inhibitor of guanylate cyclase, and ATP-sensitive K^+ channels channel blocker also inhibited the [6]-gingerol-induced anti-allodynic effect.

Borgonetti et al. [38] used SNI-induced animal models of pain to confirm the analgesic effect of single and multiple administration of *Z. officinale*. First, the acute oral administration of *Z. officinale* significantly increased the threshold to mechanical stimuli, which was reduced after surgery. In their second experiment, the repeated oral administration of *Z. officinale* for 7 days starting from 3 days after surgery significantly decreased the

pain induced by mechanical stimuli. Among the three doses used in the study (100, 200 and 400 mg/kg), the anti-allodynia effect of 200 mg/kg was greater, which was similar to 30 mg/kg of pregabalin. The increase in histone deacetylase 1 (HDAC1) in BV2 cell and spinal cord after nerve injury were not shown in single and repeated *Z. officinale* treated rodents. Moreover, acute *Z. officinale* application decreased both phosphorylated extracellular signal-regulated kinase 1/2 (pERK1/2) activation in BV2 cell and spinal cord, respectively; however, repeated *Z. officinale* treatments decreased pERK2 activation in the spinal cord. Montserrat-de la Paz et al. [35] did not use a surgical model, but exposed rodents to intermittent cold places (ICS) to assess the effect of *Z. officinale* against mechanical pain. *Z. officinale* (0.5 and 1%) was given in combination with the standard diet that initiated eight weeks before inducement of hyperalgesia, and the result shows that it dose-dependently alleviated mechanical pain. In their study, paracetamol was also treated in combination with *Z. officinale* and the co-administration-treated group mice showed less pain than individually administered littermates.

Contrasting to the above-mentioned studies, Lee et al. [31] demonstrated the effect of *Z. officinale* in chemotherapy-induced mechanical pain. As a chemotherapeutic agent, they used oxaliplatin (single, intraperitoneal injection, i.p.; 6 mg/kg), which is a widely used anti-cancer agent to treat colorectal and breast cancer. Mechanical pain induced by oxaliplatin lasted from three to five days after the injection. *Z. officinale* was orally administrated for three days after oxaliplatin injection and *Z. officinale* significantly attenuated mechanical pain for 1 h. In addition, to confirm the mechanism of the analgesic effect of *Z. officinale*, Lee et al. focused on the role of serotonin receptors present in the spinal cord, as various serotonin receptors are reported to take part in pain pathways. Intrathecal injections of 5-HT_{1A} receptor antagonist before the treatment of *Z. officinale* blocked its analgesic effect. Moreover, the spinal expression of the 5-HT_{1A} receptor was significantly decreased after oxaliplatin injection, whereas *Z. officinale* treatment reversed the decreased mRNA expression level of the 5-HT_{1A} receptor. In addition, Kim et al. [45] also reported that [6]-shogaol could significantly attenuates mechanical pain in neuropathic pain induced by oxaliplatin as in the study of Lee et al. [31]. In this experiment, [6]-shogaol was intraperitoneally injected four days after oxaliplatin injection. One hour after the administration of [6]-shogaol, the threshold to mechanical stimuli was significantly increased compared to that of the oxaliplatin group. As the mechanism of action of [6]-shogaol, authors have demonstrated that the effect of [6]-shogaol was blocked by the intrathecal injection of 5-$HT_{1A,3}$ and $GABA_B$ receptor antagonists. Moreover, treatment of [6]-shogaol increased spinal GABA and glutamate decarboxylase 65 (GAD65) protein concentration in the spinal dorsal horn of L4–5 segments. Altogether, these results suggest that *Z. officinale* and its sub-components use spinal serotonergic pathways to induce an analgesic effect.

In two studies conducted by Fajrin et al. [43,44], STZ-induced animal models of diabetic pain were used to assess the pain-decreasing effect. In their first study [43], *Z. officinale* and [6]-shogaol significantly attenuated mechanical pain induced by 110 mg/kg of STZ injection. Moreover, both *Z. officinale* and [6]-shogaol demonstrated less damage in the sciatic nerve's morphology compared to the STZ group. In their second study [44], both *Z. officinale* and [6]-shogaol significantly decreased mechanical pain induced by STZ injection. They reported that both *Z. officinale* and [6]-shogaol could significantly reduce upregulated spinal TRPV1 and N-methyl D-aspartate receptor subtype 2B (NMDAR2B) mRNA expression after STZ treatment.

Hitomi et al. [41] assessed the effect of [6]-gingerol and [6]-shogaol in 50% acetic acid filter paper-induced oral ulcerative mucositis (OUM) pain rats. In this study, the swab application of 300 and 150 μM of [6]-gingerol and [6]-shogaol, respectively, failed to attenuate the pain. However, when 13.5 mg/mL of ginseng was applied together, the mechanical threshold significantly increased and spontaneous mouth rubbing decreased Additionally, both [6]-shogaol and [6]-gingerol at 100 μM exhibited significant antagonistic effects on the $Na_v1.8$ currents and decreased substance P (SP) release induced by KCL and veratridine in CHO cells.

In summary, the above-mentioned studies demonstrate that *Z. officinale* and its main physiological active indicators, [6]-gingerol and [6]-shogaol, could significantly attenuate mechanical pain that has been induced by various animal models of pain.

Table 1. Summary on the effect of *Z. officinale* on pain.

Authors	Strain	Pain	*Z. officinale* Roscoe	Findings		
			Rats			
Sepahvand et al., 2010 [33]	Wistar Rat	Tail-Flick Test	200, 400 and 600 mg/kg (i.p. 80% Ethanol Extract)	Control:	Heat Pain	-
				Z. officinale:		↓
				Z. officinale + Morphine (2.5 mg/kg):		↓
				Mechanism of Actions:		-
Darvishzadeh-Mahani et al., 2012 [34]	Wistar Rat	Tail-Flick Test	50 and 100 mg/kg (p.o. 96% Ethanol Extract)	Control:	Heat Pain	↑
				Z. officinale:		↓
				Mechanism of Actions:		-
			Mice			
Y et al., 2002 [32]	Swiss Mice	Acetic Acid 3% (i.p.)	50 and 100 mg/kg (i.p., 100% Ethanol Extract)	Control:	Spontaneous Pain	↑
				Z. officinale:		↓
				Aspirin (150 mg/kg, i.p.):		↓
				Mechanism of Actions:		-
Ojewole 2006 [19]	Balb C Mice	Acetic Acid 3% (i.p.) and Hot Plate Test	100, 200, 400 and 800 mg/kg (i.p. 96% Ethanol Extract)	Control:	Spontaneous and Heat Pain	↑
				Z. officinale:		↓
				Morphine (10 mg/kg, i.p.): Diclofenac (100 mg/kg, i.p.):		↓
				Mechanism of Actions:		-
Montserrat-de la Paz et al., 2018 [35]	C57BL/6J Mice	ICS-induced FMS models	0.5 and 1% (p.o. Mixed with Standard Diet)	Control:	Cold, Heat and Mechanical Pain	↑
				Z. officinale:		↓
				Z. officinale + Paracetamol:		↓
				Mechanism of Actions:		-
Fajrin et al., 2019 [36]	Mice	CFA 40 µL (Intraplantar Injection) and PSNL	100, 200, 400 and 600 mg/kg (p.o., Destilator with Aquadest)	Control:	Heat Pain	↑
				Z. officinale:		↓
				Mechanism of Actions:		-

Table 1. *Cont.*

Authors	Strain	Pain	*Z. officinale* Roscoe	Findings		
Kravchenko et al., 2019 [37]	White Mice	AITC 0.5% (Subplantar Injection)	0.0125, 0.025, 0.05, 0.1, 0.5, 1 and 5% of Extract Ointment	Control:	Spontaneous Pain	↑
				Z. officinale:		↓
				Benzocaine (Ointment):		↓
				Mechanism of Actions:	-	
Fajrin et al., 2019 [43]	Balb/c Mice	STZ 110 mg/kg (i.p.)	100, 200 and 400 mg/kg (p.o., 96% Ethanol Extract)	Control:	Heat and Mechanical Pain	↑
				Z. officinale:		↓
				Gabapetin (100 mg/kg, p.o.):		↓
				Mechanism of Actions:	Prevention of sciatic nerve damage	
Fajrin et al., 2020 [44]	Balb/c Mice	STZ 110 mg/kg (i.p.)	100, 200 and 400 mg/kg (p.o., 96% Ethanol Extract)	Control:	Heat and Mechanical Pain	↑
				Z. officinale:		↓
				Gabapetin (100 mg/kg, p.o.):		↓
				Mechanism of Actions:	↓ TRPV1 and NMDAR2B mRNA expression (spinal cord)	
Borgonetti et al., 2020 [38]	CD1 Mice	SNI	200 and 400 mg/kg (p.o., Supercritical CO_2 extraction)	Control:	Mechanical and Heat Pain	↑
				Z. officinale:		↓
				Pregabalin (30 mg/kg, p.o.):		↓
				Mechanism of Actions:	↓ pERK1/2 activation (in BV2 cells and spinal cord) ↓ HDAC1 expression (in BV2 cells and spinal cord)	
Lee et al., 2021 [31]	C57BL/6 Mice	Oxaliplatin 6 mg/kg (i.p.)	100, 300 and 500 mg/kg (p.o., 100% Water Extract)	Control:	Cold and Mechanical Pain	↑
				Z. officinale:		↓
				Mechanism of Actions:	Analgesic Effect Blocked by Mixed 5-HT_1 and 5-HT_2 receptor, 5-HT_{1A} and 5-HT_3 antagonists' injections (i.t.) ↑ mRNA expression level of 5-HT_{1A} receptor	

Abbreviations: 5-HT (serotonin), AITC (allyl isothiocyanate), CFA (completed Freud's Adjuvant), FMS (fibromyalgia syndrome), GR (ginger rhizome), HDAC (histone deacetylase), ICS (intermittent cold stress), i.p. (intraperitoneal), i.t. (intrathecal), NMDAR2B (N-methyl-D-aspartate receptor subunit 2B), mRNA (messenger RNA), pERK (phosphorylated extracellular signal-regulated kinase), p.o. (per os), PSNL (partial sciatic nerve ligation), SNI (spared nerve injury), STZ (streptozotocin), TRPV1 (transient receptor potential vanilloid 1), and *Z. officinale* (*Zingiber officinale* Roscoe).

Table 2. Summary on the effect of [6]-gingerol and [6]-shogaol on pain.

Authors	Strain	Pain	Treatments	Findings		
Rats						
Gauthier et al., 2012 [40]	SD Rat	CCI	[6]-Gingerol 10 µg (i.t.)	Control:	Heat and Mechanical Pain	↑
				[6]-Gingerol:		↓
				Cyclodextrin Formulation (20 µL, i.t.):		↑
				Mechanism of Action:	-	

Table 2. *Cont.*

Authors	Strain	Pain	Treatments	Findings	
Hitomi et al., 2017 [41]	Wistar Rat	OUM	[6]-Shogaol 150 µM [6]-Gingerol 300 µM (Swab Application)	Control:	↑
				[6]-Shogaol + [6]-Gingerol:	Mechanical Pain -
				Mechanism of Action:	↓ Evoked currents on $Na_v1.8$. (CHO cell) ↓ SP release (CHO cells)
Mata-Bermudez et al., 2018 [42]	Wistar Rat	SNL	[6]-Gingerol 1, 3, 6 and 10 µg/rat (i.t.)	Control:	↑
				[6]-Gingerol:	Mechanical Pain ↓
				Gabapentin (100 µg/rat, i.t.):	↓
				Mechanism of Action:	Effect not blocked by nonselective opioid receptor antagonist (naloxone, i.t.) Effect blocked by nonselective 5-HT, $5\text{-HT}_{1A,\ 1B,\ 1D,\ 5A}$ receptor antagonists (methiothepin, WAY-100635, SB-224289, BRL-15572, SB-659551, i.t.) Effect blocked by nonselective NO synthase inhibitor, inhibitor of guanylate cyclase, channel blocker of ATP-sensitive K^+ channels (L-NAME, ODQ, glibenclamide, i.t.)
Mice					
Young et al., 2005 [39]	ICR Mice	Acetic Acid 1% (i.p.) and 10% Formalin (s.c.)	[6]-Gingerol 25 and 50 mg/kg (i.p.)	Control:	↑
				[6]-Gingerol:	Spontaneous Pain ↓
				Indomethacin (10 mg/kg, i.p.):	↓
				Mechanism of Action:	-
Fajrin et al., 2019 [43]	Balb/c Mice	STZ 110 mg/kg (i.p.)	[6]-Shogaol 5, 10 and 15 mg/kg (p.o.)	Control:	↑
				[6]-Shogaol:	Heat and Mechanical Pain ↓
				Gabapentin (100 mg/kg, p.o.):	↓
				Mechanism of Action:	Prevention of sciatic nerve damage
Fajrin et al., 2020 [44]	Balb/c Mice	STZ 110 mg/kg (i.p.)	[6]-Shogaol 5, 10 and 15 mg/kg (p.o.)	Control	↑
				[6]-shogaol	Heat and Mechanical Pain ↓
				Gabapentin (100 mg/kg, p.o.)	↓
				Mechanism of Action	↓ TRPV1 and NMDAR2B mRNA expression (spinal cord)
Kim et al., 2022 [45]	C57BL/6 Mice	Oxaliplatin 6 mg/kg (i.p.)	[6]-Shogaol 10 mg/kg (i.p.)	Control:	Cold and Mechanical pain: ↑
				[6]-shogaol:	↓
				Mechanism of Action:	Effect blocked by $5\text{-HT}_{1A,\ 3}$ receptor antagonists (NAN-190, MDL-72222, i.t.) Effect blocked by $GABA_B$ receptor antagonist (CGP 55845, i.t.) ↑ GABA and GAD65 concentration (spinal cord)

Abbreviations: 5-HT (serotonin), ATP (adenosine triphosphate), GABA (gamma-aminobutyric acid), GAD65 (glutamate decarboxylase 65), i.p. (intraperitoneal), i.t. (intrathecal), L-NAME (Nω-nitro-L-arginine methyl ester), NMDAR2B (N-methyl-D-aspartate receptor subunit 2B), NO (nitric oxide), ODQ (1H-[1,2,4]oxadiazolo [4,3-a]quinoxalin-1-one), OUM (oral ulcerative mucositis), p.o (per os), CCI (chronic constriction injury), SNL (spinal nerve ligation), SP (substance P), STZ (streptozotocin), TP (test pulse), and TRPV1 (transient receptor potential vanilloid 1).

2.2. Spontaneous Pain

Spontaneous pain includes sensations of stabbing, shooting, burning and paroxysmal pain associated with dysesthesia or paresthesia [60]. Paresthesia and dysesthesia, one of the symptoms of neuropathic pain, is spontaneous, and the cause of this sensation seems to be a spontaneous firing of nerve sprouts that changed the innervation area of peripheral nerves, and sensitization of Aβ and C-fibers [60]. However, it is still unclear whether A- or C-fibers, injured or uninjured fibers, are more important for spontaneous pain generation [61]. It has been also reported that ethological activity in nerve-end neuroma, DRG, and the thalamus

can be the basis for spontaneous pain [62]. Chronic inflammatory and neuropathic pain is clinically characterized by a type of spontaneous pain [63].

In this section, various types of chemicals, such as acetic acid [19,32,39], formalin [39] and allyl isothiocyanate (AITC) [37] were used to induce spontaneous pain in rodents, and writhing or licking response was measured to assess the spontaneous pain [19,32,37,39].

Y et al. [32], Ojewole [19] and Young et al. [39] all used acetic acid to induce spontaneous pain in mice. Intraperitoneal injection of acetic acid is known to cause inflammation of the abdominal cavity and induce writhing behavior due to visceral stimulus [64]. Y et al. [32] reported that *Z. officinale* could prevent acetic acid-induced spontaneous pain in mice. Spontaneous pain was induced by intraperitoneal injection of 3% acetic acid (i.p.), and increase in the number of abdominal constrictions (writhing) and stretching with a jerk of the hind limb were shown after the injection. *Z. officinale* was intraperitoneally injected 1 h before acetic acid administration, and it significantly prevented acetic acid-induced writhing. The effect of *Z. officinale* was similar to the effect of 150 mg/kg of aspirin, which was used as a positive control. In the work of Ojewole [19], writhes induced with acetic acid were recorded for 20 min after intraperitoneal injection of 3% acetic acid. *Z. officinale* was administrated (i.p.) 20 min preceding the acetic acid injection, and it significantly decreased acetic acid-induced writhes.

Young et al. [39] reported that [6]-gingerol has an analgesic effect in both acetic acid and formalin-induced spontaneous pain in mice. Five minutes after intraperitoneal injection of 1% acetic acid, the number of writhing increased during the following ten min. [6]-gingerol was injected intraperitoneally 30 min prior to acetic acid injection, and it significantly attenuated the writhing response. In their subsequent study, 1% formalin (20 µL) was injected to the dorsal surface of the right hind-paw to induce spontaneous pain, and the amount of time spent licking or biting the hind-paw was recorded for 40 min. The formalin test is divided into early and late phases. The early phase is caused by C-fiber activation due to peripheral stimulation, and the late phase is known to be caused by inflammatory reactions in peripheral tissues and functional changes in spinal dorsal horn [65]. [6]-gingerol and indomethacin were, respectively, administered 30 min before formalin injection. Both [6]-gingerol and indomethacin significantly attenuated the late phase (period between 15 and 40 min post formalin injection), but not the early phase (first 5 min post formalin injection) of 1%-formalin-induced licking time.

In the study of Kravchenko et al. [37], external application of *Z. officinale* as ointments, attenuated the AITC-induced spontaneous pain. AITC (0.5%, 20 µL) was injected in the sub plantar region of mice to induce spontaneous pain, and a total time spent by the animal on licking the affected limb was observed for ten minutes. *Z. officinale* ointment was applicated five to ten minutes before the injection of AITC, and a different concentration of *Z. officinale* extracts showed an analgesic effect in the group that applied ointments ten minutes before the AITC injection. Among them, 0.05% ointment observed the highest level of analgesic activity.

Altogether these four studies suggest that *Z. officinale* and [6]-gingerol could be used to attenuate the spontaneous pain induced with acetic acid and formalin injection as the writhing and licking the affected limb decreased as much as the conventionally used drugs, such as aspirin [66], diclofenac [19] and indomethacin [39], which were used as positive controls in the included studies.

2.3. Thermal Pain

Thermal pain is a common symptom both to neuropathic pain caused by nerve injury and systemic inflammatory disorders [67,68]. It refers to a change in perception of temperature, which increases sensitivity to noxious heat or cold and it also typically involves recognizing "warm" or "cold" stimuli as painful [66]. C-fiber nociceptors, non-myelinated neurons among nociceptors present in the skin, are known to mediate thermal pain sensitivity [48]. In addition, the behavioral detection response (i.e., a stabbing pain caused by heat and cold) induced by harmful radiant skin heating appears to also be

mediated by Aδ nociceptor activation [69]. The reaction of myelinated Aδ-fibers to noxious heat indicates a sense of pain at a threshold of 43 to 45 °C [70], whereas C-fiber nociceptors have a pain sensing threshold value of 41 °C on average [71]. TRPV1, also known as the capsaicin receptor, is known as the major molecular transducer of polymodal nociceptors that detect heat [72]. In humans, the innocuous cold mainly activates myelinated Aδ-fibers, and the noxious cold activates both polymodal C-fibers and Aδ-fibers. Additionally, transient receptor potential melastatin 8 (TRPM8), a non-selective cation channel, is known as the main mechanism of cold sensing in peripheral neurons [73].

In this section, thermal pain was induced by nerve injury (i.e., CCI [40], PSNL [36], ICS [35] and SNI [38]) or chemical (i.e., complete freund's adjuvant (CFA) [36], STZ [43,44] and oxaliplatin [31,45]) injections, and thermal pain was measured by using hot-plate [19,35,36,44], tail-flick [33,34,43], hargreaves [38,40], immersion [35] and acetone drop tests [31,45].

Three studies observe the effect of *Z. officinale* and [6]-gingerol in nerve-injury-induced thermal pain (SNI, CCI, and PSNL). First, Borgonetti et al. [38] demonstrated the analgesic effect of *Z. officinale* in SNI-induced thermal pain in mice. Heat pain was evaluated by using hargreaves' plantar test. SNI-induced thermal pain lasted till 21 days after the nerve injury. *Z. officinale* was injected orally at day seven after surgery, and 200 mg/kg of *Z. officinale* completely attenuated the heat pain. The analgesic effect of 200 mg/kg *Z. officinale* was similar to that of the pregabalin. Second, Gauthier et al. [40] reported the effect of [6]-gingerol in CCI-induced thermal pain. Thermal hyperalgesia was evaluated by hargreaves test, and tests were conducted at 30 min, 2 h and 4 h following intrathecal injections of [6]-gingerol (10 µg) on both paws. The results show that [6]-gingerol could attenuate thermal hyperalgesia from 30 min to 2 h and 4 h after its administration. Finally, Fajrin et al. [36] analyzed the effect of *Z. officinale* in PSNL- and CFA-induced neuropathic and inflammatory pain mice, respectively. The PSNL model ligates 1/3–1/2 of the sciatic nerve to induce pain, and it is known to be associated with the development of spontaneous pain, allodynia and hyperalgesia. However, it is difficult to associate PSNL injuries with specific DRG or spinal levels due to a random mixture of injured L4-5 spinal nerves [74]. *Z. officinale* was orally injected once a day for seven consecutive days a week after the inducement of heat pain by CFA injection and PSNL. Their results show that *Z. officinale* administration significantly increased the latency time toward thermal stimulus. The 200 mg/kg dose was the most effective in PSNL-induced neuropathy pain, whereas the 400 mg/kg dose was the most effective in CFA-induced inflammatory pain. Montserrat-de la Paz et al. [35] used ICS-induced FMS models to observe the effect of *Z. officinale* on thermal pain. Symptoms of FMS include thermal allodynia or hyperalgesia, and hot plate test or tail immersion test was used for evaluation, respectively. *Z. officinale* (0.5 and 1%) and paracetamol were supplied in combination with the standard diet daily that initiated eight weeks prior the inducement of pain. In the hot plate test, only *Z. officinale* (0.5%) and co-administrated group significantly decreased the thermal hyperalgesia. However, in the tail immersion test, the *Z. officinale* (0.5 and 1%) alone group was effective in both cold and hot pain (allodynia and hyperalgesia).

Chemotherapy treatment is also known to induce thermal pain both in humans and rodents [75,76]. In the study of Lee et al. [31] and Kim et al. [45], cold pain was assessed by using the acetone drop test. Lee et al. [31] injected different doses of *Z. officinale* orally in oxaliplatin-induced neuropathic pain, and all doses succeeded in significantly attenuating cold pain when measured 60 min after its administration. Kim et al. [45] also reported that [6]-shogaol could significantly alleviate cold pain in neuropathic pain induced by oxaliplatin. [6]-shogaol was injected intraperitoneally, and analgesic effect was shown 60 min after the administration. Fajrin et al. reported two studies related to thermal pain; on the first study [43], the efficacy of *Z. officinale* and [6]-shogaol were evaluated through a tail-flick test in the STZ-induced heat pain in mice. Oral and intraperitoneal administration of *Z. officinale* and [6]-shogaol, decreased thermal hyperalgesia, respectively. In their subsequent study [44], STZ was also used to induce thermal pain (heat), and the hot-plate test was used to evaluate the analgesic effect of *Z. officinale* and [6]-shogaol. The

results show that both *Z. officinale* and [6]-shogaol treated group mice showed significantly longer latency time toward thermal stimulus compared to the diabetic control group.

Ojewole [19] and Sepahvand et al. [33] evaluated the effect of *Z. officinale* in electrical and radiant heat-induced thermal pain using a hot plate test and a tail flick test, respectively. In the study of Ojewole, *Z. officinale* was intraperitoneally administrated 20 min before the hot-plate test, and jumping-out of the beaker was considered a response to heat-induced pain. *Z. officinale* treatment significantly delayed the reaction time induced by electrical heat. Sepahvand et al. [33] also demonstrated the effect of *Z. officinale* through a tail-flick test in radiant heat-induced pain in rats. The tail-flick test was evaluated after intraperitoneal injection of the *Z. officinale* or morphine. *Z. officinale* was injected 15 min before morphine injection to confirm the effect of co-administration in morphine analgesia. *Z. officinale* exerted an analgesic effect in tail-flick test, which peaked at 30 min after injection and lasted till 60 min. The analgesic effect of *Z. officinale* peaked at 30 min after the injection and lasted till 120 min, respectively (120 mg/kg). Morphine alone showed no analgesic effect; however, co-administration of *Z. officinale* (200 mg/kg) and morphine produced an antinociceptive effect that lasted 120 min. As a result, the analgesic effect of *Z. officinale* alone or with morphine was greater than the morphine.

Darvishzadeh-Mahani et al. [34] have reported that *Z. officinale* could protect the development of morphine-induced tolerance in radiant heat-induced pain (tail-flick test). The tolerance of analgesic effect was demonstrated by multiple injections of morphine (twice a day for eight days). *Z. officinale* was given through the oral route and co-administered with morphine. Concomitant treatment of morphine and *Z. officinale* significantly prevented the morphine-induced tolerance. Dose of 25 mg/kg of *Z. officinale* shows anti-tolerance effect, whereas 10 mg/kg *Z. officinale* failed to show a significant effect. In addition, co-administration of morphine and *Z. officinale* (100 mg/kg) reversed the morphine-induced L-type calcium channel over-expression in the spinal cord.

Altogether, the results demonstrated in the included studies clearly show that *Z. officinale*, [6]-gingerol and [6]-shogaol can effectively attenuate thermal pain (i.e., cold and heat) induced by nerve injury and chemotherapy treatment.

3. Discussion

In this study, the effect of *Z. officinale*, [6]-gingerol and [6]-shogaol on different types of pain have been summarized. A total of 16 studies that focused on *Z. officinale* [19,31–38], [6]-gingerol [39–42] and [6]-shogaol [43–45] have been included. To our knowledge, this is the first time that their effect and underlying mechanism of action in pain have been analyzed. *Z. officinale* is widely known for its effect on the digestive system, and it has been mainly used to treat digestive disorders [77–79]; however, recent clinical [80,81] and animal [82–84] studies suggest that it could also be effective against the pain, but too little is known on their effect and mechanisms of action.

Z. officinale, ginger, which has long been widely used to treat various diseases, is one of the most popular herbal dietary supplements in the world [85]. It is also known to cause no severe side effects, and the U.S. Food and Drug Administration (FDA) classified ginger as "generally recognized as safe" [86]. The components of *Z. officinale* include volatile oils, fixed fatty oils and pungent compounds but depends on the characteristics of the cultivated region, agroclimatic conditions [87]. As the pungent compounds, [6]-gingerol and [6]-shogaol, are the two main compounds [88]. When gingerol, which is unstable in heat, is deformed at a high temperature, it becomes shogaol, and [6]-shogaol is the most common dehydrated product [89]. Although the content of [6]-gingerol and [6]-shogaol in *Z. officinale* appears to be affected by drying and extraction temperatures [89], it is reported that about 11% and 0.08% are contained in *Z. officinale*, respectively [90]. Both shogaols and gingerols are known to easily pass the blood–brain barrier (BBB) [91].

In this study, the analgesic effect of *Z. officinale*, [6]-gingerol and [6]-shogaol have been analyzed on mechanical, spontaneous, and thermal allodynia or hyperalgesia (Tables 1 and 2), and different animal models of pain have been used. Among the 16 studies included, five

used different types of nerve injury pain models, whereas 11 used diverse chemicals to induce pain in rodents. On mechanical allodynia, five studies focused on the effect of *Z. officinale* and four on [6]-shogaol and three on [6]-gingerol. On spontaneous pain, three observed the pain-decreasing effect of *Z. officinale* and one of [6]-gingerol. Finally, on thermal pain, nine reported the action of *Z. officinale* and one and three of [6]-gingerol and [6]-shogaol, respectively.

In the included studies, only seven papers have demonstrated the underlying mechanism of action of the analgesic effects of *Z. officinale*, [6]-gingerol and [6]-shogaol [31,38,41–45]. Five studies have focused on the spinal cord, one on the DRG neurons and one has used cultured cell. Three studies [31,42,45] focused on the role of spinal serotonergic receptors [31,42,45], and spinal TRPV1, spinal NMDA receptor (NMDAR) [44], spinal pERK1/2, histone deacetylase (HDAC1) [38], spinal pERK1/2, histone deacetylase (HDAC1), sciatic nerve's morphology [43], and $Na_v1.8$ and SP [41] have been observed by one study (Figure 2).

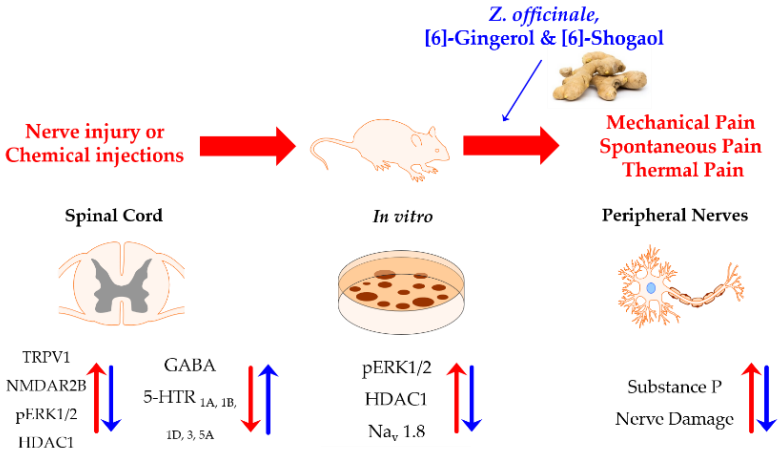

Figure 2. The pathogenesis mechanism of pain induced by nerve injury or chemical injection and the mechanism of action of the analgesic effect of *Z. officinale*, [6]-gingerol and [6]-shogaol. Pain is caused by nerve injury or chemical injection (Red), and pain is attenuated when *Z. officinale* and its sub-components are administered (Blue). Mechanism was identified on the spinal cord, peripheral nerves and cultured cell (in vitro). Abbreviations:5-HTR (serotonin receptor), GABA (gamma-aminobutyric acid), HDAC1 (histone deacetylase 1), $Na_v1.8$ (voltage-gated sodium channel 1.8), NMDAR2B (N-methyl-D-aspartate receptor subunit 2B), pERK (phosphorylated extracellular signal-regulated kinase), TRPV1 (transient receptor potential vanilloid 1), and *Z. officinale* (*Zingiber officinale* Roscoe).

To assess the involvement of the serotonergic system, Lee et al. [31], Kim et al. [45] and Mata-Bermudez et al. [42] observed the role of serotonergic receptors in the spinal cord. On the oxaliplatin-induced animal model of pain, both Lee et al. and Kim et al. have reported that intrathecal pre-treatment of 5-HT_{1A} and 5-HT_3 receptor antagonists could block the analgesic effect of *Z. officinale* and [6]-shogaol. Although the animal model of pain was different (oxaliplatin vs. SNL), Mata-Bermudez et al. have also focused on spinal 5-$HT_{1A, B, D,}$ and $_{5A}$ receptors and demonstrated that the analgesic effect of intrathecal injection of [6]-gingerol is mediated by these receptors. In addition, in the study of Kim et al. [45], [6]-shogaol was shown to decrease both the mechanical and cold pain through spinal 5-HT_{1A} and 5-HT_3 receptors present in the spinal GABA neurons, which are inhibitory interneurons [45]. Altogether, these results suggest that both *Z. officinale* and [6]-shogaol act on spinal 5-HT_{1A} and 5-HT_3 receptors and [6]-gingerol on spinal 5-$HT_{1A, B, D,}$ and $_{5A}$ receptors. Seven families of serotonin recipients are divided into 15 subtypes [92], and are found in both central and peripheral nervous systems [93]. Among them, 5-HT_3 receptors are ligand-gated ion channels (LGICs), whereas other receptors are G-protein-coupled receptors (GPCRs) [92]. 5-$HT_{1, 3}$ and $_5$ receptors are known to be present in the superficial laminae of the dorsal horn of the spinal cord and are reported to induce an analgesic effect upon activation [94–96]. Although the included studies have demonstrated that *Z. offici-*

nale and its sub-components could induce analgesic effect through serotonergic receptors present in the spinal cord, much remains to be clarified, as whether they directly activated these receptors or indirectly activated them by increasing the synthesis of descending serotonin from the rostro ventromedial medulla (RVM) of the brain has not been understood yet. Thus, further studies are needed to clearly understand the role of the serotonergic system in the analgesic effect of *Z. officinale* and its sub-components.

In the study conducted by Fajrin et al. [44], the role of spinal TRPV1 has been observed. [6]-Gingerol and [6]-shogaol are known as capsaicin structural analogs [97] and have a high binding affinity for TRPV1 [98]. By using a diabetic induced animal model of pain, Fajrin et al. has reported that *Z. officinale* and [6]-shogaol modulate the expression of spinal TRPV1 to induce analgesia. They reported that both *Z. officinale* and [6]-shogaol decrease the expression of TRPV1 in the spinal cord. Compared to the relatively well understood role of the TRPV1 present on the peripheral nervous system, the role of spinal TRPV1 has not been clearly understood yet [99,100]. In the spinal cord, TRPV1 is known to exist in the superficial laminae I and II, which are pain sensory pathways [101]. Kanai et al. [102] confirmed a gradual increase in TRPV1 expression in superficial dorsal horns of spinal cord in the CCI rats model and reported that intrathecal administration of TRPV1 antagonist could induce analgesia. In addition, mechanical and heat hypersensitivity induced by spinal cord injury were reversed by intrathecal injection of antisense oligonucleotide, which knockdown spinal TRPV1 [103]. In clinical trials, the TRPV1 antagonist has been reported to significantly increase the threshold for capsaicin-induced heat and pressure pain in healthy volunteers [104]. TRPV1 has also been reported to be related to the activity of spinal astrocytes [105] and microglia [106] augmenting the ascending neuronal pain signals transmitted to the brain. Furthermore, TRPV1 can interact with NMDAR2B to contribute to pain development [107], as a study has reported that spinal TRPV1 expression was increased in carrageenan-inducted pain condition, and expression of TRPV1 and phosphorylated NMDAR2B decreased when capsazepine, the TRPV1 antagonist, was intrathecally administered [108]. Furthermore, *Zingiber zerumbet*, which is a different species of the Zingiberaceae family [109], has also shown an antinociception effect similar to capsazepine [110]. They further revealed that the antinociception effect of *Zingiber zerumbet* is mediated through the NO and adenosine triphosphate (ATP)-sensitive K^+ channel pathway. The opening of the ATP-sensitive K^+ channel, which releases K^+, leads to a decrease in membrane excitability through membrane repolarization or hyperpolarization [111]. Similarly, Mata-Bermudez et al. [42] have demonstrated that [6]-gingerol affected the NO–cyclic guanosine monophosphate–ATP-sensitive K^+ channel pathway to induce analgesia. In addition to the above-mentioned mechanisms, calcitonin gene-related peptide (CGRP) has been reported to be modulated by *Z. officinale,* as an in vitro study has suggested that *Z. officinale* could attenuate the trigeminal pain by modulating CGRP [112]. CGRP is known as the main inflammatory mediator in neurogenic inflammation of migraine. Peripheral release of CGRP is known to be involved in the development and maintenance of central sensitization and allodynia, and receptor antagonist of CGRP is targeted as a treatment for migraine and chronic pain [113]. TRPV1 expressed in trigeminal nociceptors has also been reported to cause neurogenic inflammation by releasing CGRP [114].

In conclusion, based on the results obtained from 16 studies, our review suggests that *Z. officinale* and its sub-components (i.e., [6]-gingerol and [6]-shogaol), which have long been used as herbal medicines, can be used to treat mechanical, spontaneous, and thermal (cold and heat) pain. However, more studies that focus on the mechanism of action are still needed, as the understanding of the underlying mechanism of action is still poor, especially on the role of the serotonin system and TRPV1. Furthermore, future studies should focus not only on the spinal cord, but also on the brain and the peripheral nervous system to enlarge the understanding on the effect of *Z. officinale.*

4. Materials and Methods

A search was conducted on all studies on the effect of *Z. officinale* and its subcomponents of pain in the National Library of Medicine (MEDLINE) using PubMed, and Google Scholar (Figure 3). Extensive searches were undertaken for articles written in English, as non-English studies were excluded. Studies electronically published until the end of June 2022 were included. The literature search was performed using the following keywords: "*Zingiber officinale* roscoe (*Z. officinale*)", "[6]-Shogaol", "[6]-Gingerol", "Allodynia" and "Hyperalgesia" "Pain". After the initial search, duplicates, bibliographies, study protocols, clinical trials, and non-English studies were excluded. Sixteen animal studies were included in this study.

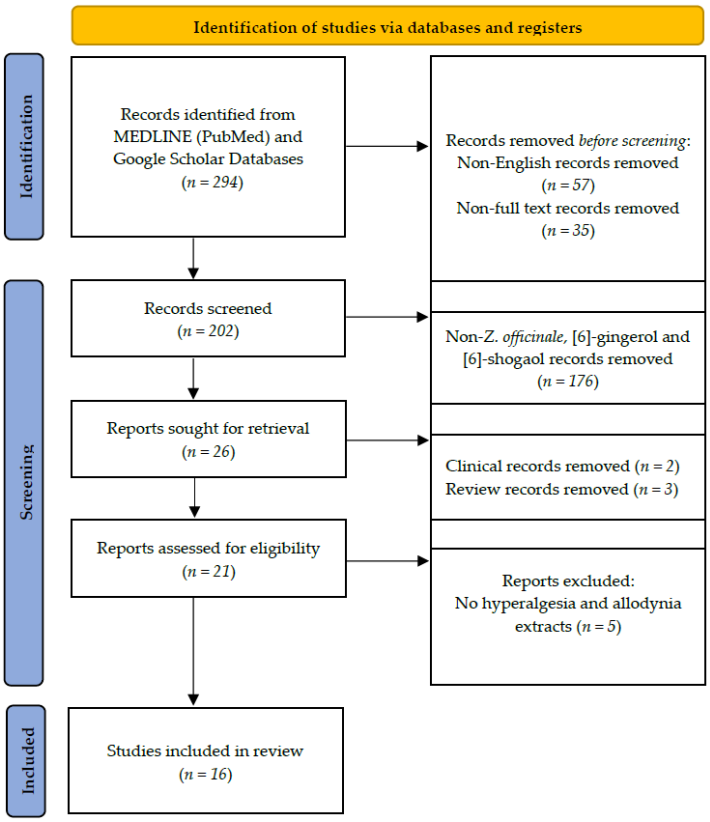

Figure 3. Flow chart of the article-inclusive protocol. Identification through searches of MEDLINE (PubMed) and Google Scholar yielded 294 articles, which were screened by abstract and full-text examinations. Finally, a total of 16 articles analyzing the effect of *Z. officinale*, [6]-gingerol and [6]-shogaol in hyperalgesia and allodynia in rodents were included in our review.

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