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EDITORIAL

Investigation of anti -nociceptive activity of Zingabeel (*Zingiber officinale*) on acetic acid induced writhing in rats

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Abstract:

This study was carried out to test for antinociceptive effect of the methanolic extract of ginger using acetic acid induced writhing in rats and compared to morphine and diclofenac sodium as standard drugs. The methanolic extract of ginger, showed dose dependent responses whereas 50 and 100mg/kg produced 100%protection against writhing induced by acetic acid (0.6 % i.p.) . This protection supersedes the effect of diclofenac sodium (25, 50 and 75 mg/kg). On the other hand morphine (2.5- 10 mg/kg), exhibited 100% protection against writhing induced by acetic acid.

Therefore we can conclude and recommend that, ginger is a potential source of new and effective anti-nociceptive agent(s). Bioassay guided fractionation for the methanolic extract of ginger should be investigated for the determination of active ingredient(s), and to elucidate their mechanism of action.

الخلاصة:

أجريت هذ الدراسة لإختبار تأثير الخلاصة الميثانولية للزنجبيل كمسكن للألم باستخدام حمض الاستيك الذي يحفز الانقباضات ألبطنيه المسببة للألم ومقارنته بالمورفين و الدايكلوفيناك صوديوم كأدوية مرجعية. أظهر المستخلص الميثانولي للزنجبيل إستجابات إعتمادا على الجرعات حيث إنه في الجرعات 50 و 100مجم/كجم نتجت حماية بنسبة 100% ضد الانقباضات المسببة بواسطة حمض الأسيتيك (0,6%)، حيث يعتبر أفضل تأثيرا من الدايكلوفيناك صوديوم (25، 50، 75مجم/كجم) ومن ناحية أخرى فإن المورفين (2.5 -10 مجم/كج) قد أعطى حماية بنسبة 100% ضد الانقباضات المسببه بواسطة حمض الأسيتيك. لذا نستنتج ونوصي بأن الزنجبيل مصدر متوقع جديد فعال كمسكن للآلام. كما نوصي بأن تجرى الاختبارات الحيوية الموجهه للتجزئة للزنجبيل لتحديد المادة الفعالة و توضيح آلية عملها.

Key words: Zingabeel, Ginger, Acetic acid induced writhing & Antinociceptive agents.

Introduction:

Ginger (*Zingiber*) is the scraped or unscraped rhizome of *Zingiber officinale* (Zingiberaceae). Common names are: ginger, ginger root, black ginger, zingiberis rhizome. Ginger is used as a common cooking spice in a variety of foods and drinks, including ginger bread, ginger snaps, ginger sticks, and ginger ale[(1)]. It is grown in many parts of the world, including Jamaica, China, India and Africa[(2)]. In the fresh ginger rhizome, the gingerols were identified as the major active components and 6-gingerol [5-hydroxy-

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1-(4-hydroxy-3-methoxy phenyl) decan-3-one] is the most abundant constituent in the gingerol series. The powdered rhizome contains fatty oil, protein, carbohydrates, crude fiber, ash, water and volatile oil. In dried ginger powder, shogaol a dehydrated product of gingerol is a predominant pungent constituent [(3)]. Ginger products are available as extracts, tinctures, capsules, and /or oils. Fresh ginger root can also be purchased and prepared as a tea[(1)]. Ginger has an antitumor activity and it has been demonstrated in several *in vitro* animal experiments. Human clinical trails have examined ginger's antiemetic effects related to motion sickness, post operative, pregnancy-related and chemotherapy related nausea and other causes. Ginger was found to produce cardio tonic, central nervous system (CNS) and enhanced testosterone production effects[(1)]. Also ginger used in asthma, athlete's foot, acne, mumps, gingivitis, ringworm (tinea), mouth ulcer and sore throat[(4)].

Pain is the most common symptoms that motivate a person to seek professional help and it differs from other sensations in that it sounds a warning that something is wrong[(5)]. Thousands of years ago, various forms of natural plant substances have been used to treat pain disorders. It was not until the 19th century when individual compounds were isolated from these substances. These compounds were determined to posses the desired effects of understanding of complex mechanisms involved in pain transmission and pain relief. They include: Salicin (Salix), morphine (Opium), tetrahydrocannabinol (Canabis) and capsaicin (Capsicum) and they showed undesirable side effects[(6,7)]. Such findings have highlighted the importance of discovering novel analgesics/ antinociceptive compounds with idealistic pharmacological profiles (no side effects, no addictive potential).

Previous clinical trials exploring the anti-inflammatory and pain–relieving effects of ginger have provided mixed results, the majority of which showing a tendancy toward pain relief greater than placebo but less than traditional anti-inflammatory drugs[(1,8)]. Ginger is reported in Ayurvedic and Tibb system of medicine to be useful in rheumatic disorders[(1,9)].Data reported by Sepahvand *et al.* (2010)[(10)] indicated that ginger extract has beneficial influence on morphine analgesia and can be an efficacious adjunct for pain management. The analgesic and anti-inflammatory effects of 6-gingerol, which is the pungent constituent of ginger, were investigated by Young *et al.*(2005) [(11)] . It was found to produce an inhibition of acetic acid induced writhing response and formalin induced licking time. In this study the methanolic extract of ginger was used to investigate the significance of this edible plant as antinociceptive drug.

Materials and Methods

Plant material: Rhizomes of the plant *Zingiber officinale* were purchased from Wad.Medani local market in June 2010.

Preparation of extract: The dried rhizomes were grind with a hammer mill to a coarse powder, 150g of the dried ginger powder was macerated in methanol (Moody Company, Saudi Arabia) over a period of 72 hours (hrs.) at room temperature. The resulted solution was filtered by filter paper (quality special 002, size 11cm), evaporated at room temperature (24 hrs) to a brown semi-solid mass, which was kept as ready for use.

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Drugs: Diclofenac sodium 75mg/5ml (Shangahi, Sudan) and morphine 10mg/ml (Darou Pakhsh, Iran) were used as standared drugs. Acetic acid (Central Drug House (P) LTD , India) was used to induce writhing in rats as 0.6% solution.

Experiments: In this study rats (150-200gm) of both sexes in five groups of rats (n=5) were used for the methanolic extract of ginger (test groups). As described by Woode, *et al.* (2009)[12], ginger was administered intraperitoneally (i.p.) for different groups (1-5) separately in doses of 5,10, 25, 50 and 100 mg extract /kg. Thirty minutes later each rat thereafter received acetic acid (0.6% i.p.) in a dose of 10 ml/kg , which known to induce writhing in rats. For the control, nine groups (n=5) were used whereas, control group A was untreated, control group B was treated with vehicle ($Tween_{20}$ 5% i.p.) 10ml/kg, while the remaining seven groups were treated with standared drugs, of which four groups received morphine (2.5, 5, 7.5 and 10 mg/kg i.p.) that known to act centrally and peripherally to relive pain and three groups received diclofenac sodium in doses of (25, 50 and 75 mg/kg i.p.) that known to act only peripherally. Acetic acid (0.6%) by i.p. route in a dose of 10 ml/kg was given for the control animals 30 minutes later. Results observed 10 minutes after acetic acid administration are presented in Table 1 as mean number of writhes ± standard deviation (SD) using SPSS version16. Percentage of protection from writhes induced by acetic acid was calculated as followed:

$$\% \text{ protection} = \frac{MWut - MWt}{MWut} \times 100$$

Where:

MWut = Mean number of writhes of an untreated group (control A).

MWt = Mean number of writhes of a treated group.

Results and Discussion:

Table (1) represents the total number of writhes induced by acetic acid 10 minutes after its administration in different groups of treated and untraeted rats during an observational period of 20 minutes.

Table 1: Effect of ginger, morphine and diclofenac on acetic acid induced writhing in rat.

Treatment	Dose (i.p.)	Mean of writhing ±SD	Protection %
Control group A (untreated)	0.00	35.4±8.56	0.00
Control group B ($Tween_{20}$ 5% - treated)	10mL/kg	33.6 ±0.577	5.08
Ginger	100 mg/kg	0 ±0	100
	50 mg/kg	0 ±0	100

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(test)	25 mg/kg	1 ±0.155	97.2
	10 mg/kg	8 ±8.49	77.4
	5 mg/kg	13 ±2.83	63.3
Diclofenac sodium (Standared drug)	75 mg/kg	1 ±0	97.2
	50 mg/kg	0.67 ±1.155	98.1
	25 mg/kg	1.66 ±2.887	95.3
Morphine (Standared drug)	10 mg/kg	0 ±0	100
	7.5 mg/kg	0 ±0	100
	5 mg/kg	0 ± 0	100
	2.5 mg/kg	0 ±0	100

Results showed that, the methanolic extract of ginger exhibted dose dependent responses whereas 50 and 100 mg/kg produced 100%protection against writhing induced by acetic acid. This protection supersedes the effect of diclofenac (25, 50 and 75 mg/kg), and equal to morphine (2.5 – 10 mg/kg i.p.) which, exhibited 100% protection against writhing induced by acetic acid in rats.

Acetic acid induces pain by releasing endogenous substances that excite pain nerve endings centrally and peripherally. The observed abdominal constriction produced by acetic acid is related to the sensitization of nociceptive receptors to prostaglandins[(11)]. Diclofenac and other non steroidal anti-inflammatoty drug (NSAIDs) are known to inhibit the number of writhes by inhibiting cyclooxygenase in peripheral tissue, thus interfering with the mechanism of transduction in primary afferent nociceptors by blocking the effect or the synthesis and/or release of inflammatory mediators (prostaglandins). Morphine acts by combining with opioid receptors, which are found in the central nervous system and the peripheral sites [(12)].This analgesic / antinociceptive effects of ginger may be attributed to the pungent constituent 6-gingerol[(11,13-16)]. It is clearly shown in (Table 1) that the effect produced by diclofenac sodium which acts only on the peripheral sites is lower than the effect produced by morphine and/or ginger, which in this sense seems to act on both central and peripheral sites of action.

Conclusion and Recommendation:

In conclusion, this study provides important information and new area for research. The edible plant, ginger in doses of 50-100 mg/kg may exhibited both peripheral and central effects as it is superior to diclofenac and equal to morphine as a potential antinociceptive agent. Bioassay guided fractionation for the methanolic extract of ginger should be investigated for the determination of active ingredient(s), and to elucidate their mechanism of action.

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