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Evaluation of Short Term Toxicities Induced by Ginger Oleoresin

Shahnaz Ahmad*, Nighat Afza, Atiq-ur-Rahman, Shamim Qureshi and Yasmeen Bader

Pharmaceutical Research Centre, PCSIR Laboratories Complex, Karachi-75280, Pakistan

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Ginger Oleoresin exhibited a marked action on central nervous system. The oleoresin was found to be non lethal upto a dose of 3.0g kg^{-1}., while a dose above that resulted in mortalities. The LD50 was found to be 6.284 g kg^{-1}. The signs and symptoms observed in non lethal doses were solely functional and short lived. The magnitude and intensities of signs and symptoms exhibited were found to be dose dependant, while lethal doses imparted pharmacological and toxicological action by affecting the physiological mechanism of the body. Death occurred may be due to the direct action on central nervous system resulting in respiratory failure as well as circulatory arrest.

Key words: Ginger, Oleoresin, Toxicity, Therapeutic dose.

Introduction

Zingiber officinale Roscoe (Scitaminaceae), a rhizome is commonly known as 'ginger' in English, 'adrak' in Urdu and 'zangabil' in Arabic (Watt 1890, Nadkarni 1954; British Herbal Pharmacopoeia 1987). Plant is indigenous to Asia but is cultivated in Pakistan, India & West Indies (Watt 1890).

Ginger has a well documented record of its preventive and ameliorative effects in various systems of treatment. It is used singly or in combination with other remedial agents topically and systemically (Nadkarni 1954; Duke and Ayensu 1985). Medicinally ginger is used as a mild laxative, emmenagogue, antispasmodic, antacid, antiulcer, disflatulent, antiemetic (Kudo and Nomura 1990; Yamahara *et al* 1990; Tariq *et al* 1993; Yoshi Kawa *et al* 1994), anti-inflammatory, antipyretic, analgesic (Nadkarni 1954; Sudhendu 1982; Suekawa *et al* 1984; Duke and Ayensu 1985; Lee Eunyong and Lee 1998) antimicrobial (Jasper *et al* 1959; Endo Katsuya *et al* 1990) antioxidant (Al- Jalay *et al* 1985; Lee Eunyong and Lee 1998; Schimuzu *et al* 1999) and as hypocholesterolemic agent (Maharaja 1978; Kudo *et al* 1990). It is also used commercially in food, beverages, cosmetics and perfumery industries (Al-Jalay *et al* 1985; Huang *et al* 1990).

Oleoresin prepared from ginger is used specially in carminatives, anti-diarrhoeal mixtures, spasmolytic preparations and in carminative beverages, (Ainley 1977; Suahendu 1982). Literature citation gives an ample data on the pharmacological (Tariq *et al* 1993) and phytochemical analysis (Al Yahya 1986) of ginger, but very few reports are available on acute and short term toxicities induced by ginger oleoresin. Therefore the present study is not only aimed to obtain and to clarify the evidences for the safe therapeutic dose of ginger oleoresin but also to determine its toxic effects.

*Author for correspondence

Materials and Methods

Preparation of extract (Oleoresin). Dry ginger was purchased from the local market, cleaned and ground to 150-mesh size. The powdered ginger was then dried in oven at 45°C±5°C for 4 h to remove the moisture. The dried powdered ginger (500g) was then extracted with di-isopropyl alcohol in a soxhlet apparatus. The solvent was removed under vacuum and 52g of the residue obtained was then extracted with acetone. The acetone soluble fraction was evaporated in a rotary evaporator. The traces of solvent were removed under high vacuum to obtain 41g of transparent light yellowish brown oleoresin which was used in the present study.

Toxicity studies. Healthy adult swiss mice of either sex, weighing 25-30g maintained on standard diet and water *ad libitum.* Animals were kept under optimal experimental conditions for a period of 3 days before use. Cages were marked with their respective doses. Each dose was repeated thrice to confirm the results.

Different concentrations (mg kg^{-1}) of ginger oleoresin suspended in 1% Tween 60 (Polyoxy ethylene monostearate) solution was administered orally by means of a gavage in a single dose in fixed volume (i.e 0.5 ml). Control group was run simultaneously using vehicle in same volume. All animals were observed carefully for gross physical and behavioural changes. Mortality rate noted, autopsy done and necroscopic findings were made to note gross drug related pathological changes. LD50 calculated by the method of Reed and Munch on the basis of 72 h mortalities (Turner 1965).

Results and Discussion

Evaluation of toxicities induced by ginger oleoresin was found to be dose dependent. Large doses of oleoresin affected physiological mechanism of the body by specific toxic action and finally culminated in death. Furthermore the severity and depth of signs and symptoms exhibited as well as subjective changes in mood and behaviour were found to be proportional to the concentration of the extract used. No mortality was observed up to a dose of 3g kg^{-1}, while doses above that resulted in mortalities.

A single dose regimen upto 0.5g kg^{-1} exhibited vasodilatation, activeness and alertness in animal, while a dose above that showed initiation of toxic signs and symptoms. The signs and symptoms exhibited were found to be dose dependant. The common manifestations observed in higher doses were irritability, restlessness, tremore, discomfort, vasoconstriction, piloerection, pallorness, abdominal discomfort, gagging, retching, excessive salivation, hiccough, tenusmus, dyspnoea, tachypnoea, loss of writhing reflexes, frequent urination, convulsion followed by muscular weakness, decrease in motor activity, sedation, hypnosis and death.

A dose of 3.5 g kg^{-1} and above caused epigastric pain and abnormal gait associated with abdominal cramps, irritation forced the animals to crawl on their abdomen in order to get some relief from abdominal irritation. The intense gastric irritation also resulted in retching and gagging. Animals showed apathy towards external stimuli at a dose of 4.5 g kg^{-1} and onwards. This apathy became more severe with the passage of time. Prior to death animal exhibited laboured respiration, convulsion, loss of response to painful stimuli, unconsciousness and coma. Diarrhoea, tenusmus and depression were observed among the survivors at a high dose level. Amelioration of all these signs and symptoms in survived animals took 9-50 min in lower doses i.e upto 3g kg^{-1} while in higher doses the recovery time was enhanced from 90-210 min. The drug was excreted in the urine after 20-30 min of feeding.

On autopsy, macroscopic finding made in dose groups ranging from 3-4. 5g kg^{-1} revealed the accumulation of clear fluid in abdominal cavity, dilation of blood vessels, few hemorrhagic spots on heart, clotting of blood in auricles, congestion of lungs and viscous clear fluid in stomach. while doses above that exhibited same findings except large quantity of turbid fluid in abdominal cavity, frequent hemorrhagic spots on heart, severely congested lungs and viscous turbid yellowish fluid along with desquamated epithelial lining in the stomach with highly acidic pH. A dose of 5g kg^{-1} and above totally exfoliate the epitelial lining of the stomach making it thin and transparent.

From the acute toxicity studies designed to express the potency of a toxic effect of ginger oleoresin in term of median lethal dose (LD 50) was 6.284g kg^{-1} which indicates that the ginger oleoresin has a great margin of safety (Table 1).

Table 1
Oral toxicity of ginger oleoresin

S.No	Dose (mg kg^{-1})	No. of animals in each group	No. of animals died	No. of animals survived	Percentage mortality
1	3000	8	0	8	0
2	3500	8	1	7	12.5
3	4500	8	2	6	25.0
4	5500	8	3	5	37.5
5	6500	8	5	3	62.5
6	7500	8	7	1	87.5
7	8500	8	8	0	100.0

Conclusion

Ginger oleoresin has a great margin of safety and has a definite action on CNS. Large doses do impart pharmacological and toxicological action by affecting physiological mechanism of the body and thus imparting specific toxic action. These actions can be avoided by proper intelligent adjustment of dose of ginger oleoresin; further more the effects exhibited by the oral use in non lethal doses are solely functional lasting only for a short period of time. The magnitude and intensities of signs and symptoms exhibited were found to be highly dose dependant.

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