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Comparative Anti-inflammatory Activity of NSAIDs and Herbal Extracts in Carrageenan-Induced Paw Edema

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***Abstract*---** To assess the anti-inflammatory properties of fresh Zingiber officinale rhizome aqueous and methanolic extracts: 1. To use the Carrageenan-induced paw edema technique to test the anti-inflammatory activity of all extracts in two dosages and the standard medication in wistar rats. 2. To contrast the two extracts' anti-inflammatory properties with those of a prescription medication. The research was carried out with consent from the animal ethics committee. There were six groups of animals. While test groups received aspirin (150 mg/kg), aqueous extract of fresh Z. officinale rhizome (100 and 200 mg/kg), and methanolic extract of fresh Z. officinale rhizome (100 and 200 mg/kg), the control group received 0.2 ml NS IP. Ginger's anti-inflammatory properties were examined using an acute model of inflammation that included rat paw edema caused by carrageenan. Aqueous and methanolic extracts of fresh rhizome had considerable anti-inflammatory effect ($p < 0.05$) in the acute model of inflammation when compared to control, and at all time intervals, their activity was equivalent to that of aspirin. Gingiber officinale extracts, both aqueous and methanolic, have strong anti-inflammatory effects.

Keywords: carrageenan, aspirin, ginger, and anti-inflammatory.

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Introduction

The term inflammation comes from the Latin word "inflammacio," which means "to set a fire." 1 Celsus, a Roman author from the first century AD, was the first to enumerate the three cardinal indications of inflammation: tumor, calor, and dolor. Calor implies heat, dolor denotes agony, and rubor indicates redness. Tumor suggests swelling. "Loss of function" is the sixth clinical symptom that Virchow introduced. 2. The body employs it as one of its defense systems to either eliminate or restrict harmful substances such as bacteria, viruses, parasites, fungus, antigen antibody complexes, etc. 3. It has been shown that medications such as non-steroidal anti-inflammatory medicines have anti-inflammatory properties. They may be used for both acute and chronic pain, and they are non-specific analgesics. 4. However, they are causing liver damage, nephrotoxicity, and peptic ulcers. On the other hand, ginger has hepatoprotective, anti-emetic, and digestive properties.

The plant known by its botanical name, Zingiber officinale (Family: Zingiberacae), is found all over the globe. 5. For over 25 centuries, it has been used as a spice and flavoring element in cuisine, as well as in traditional Chinese and Indian medicine. It is cultivated extensively in Mexico, Hawaii, Jamaica, and India. This subterranean root, also known as a rhizome, has antiemetic properties, improves blood circulation, aids with digestion, and more in traditional medicine 6. The analgesic 7,8, anti-inflammatory 9, 10, hepatoprotective 11, hypouricaemic 12, antidiabetic 13, and anticancer properties of either crude extract or pure gingerol are suggested by a number of animal investigations, human pilot studies, and clinical trials. Although several applications of crude ginger extract are referenced in traditional medicine across many nations, the use of ginger extract for acute and chronic anti-inflammatory purposes is not proven in contemporary medicine and is not recorded in textbooks. They haven't been confirmed yet. Although a few research find little action, other experimental investigations have shown its anti-inflammatory properties in animals. The development of a novel, safe medication that will help patients with pain and inflammation will advance if the anti-inflammatory properties of ginger extract are shown.

Materials and Methods

Animals

Wistar rats of either sex weighing 150-200G were procured from the Central Animal House, KIMS, Karad. Total 6 groups of animals each having 6 animals were used for experiments. Total 36 wistar rats were used.

Drugs

Fresh rhizome of Zingiber officinale was obtained from local market. The rhizome was used after authentication by botanist. The rhizome was washed with tap water and shade dried. Aqueous and methanolic extracts of both powders were prepared by using Soxhlet Apparatus. All dried extracts were dissolved in 0.9 % normal saline for injection intraperitoneally. Following extracts and standard drug were used in two doses as given in following table.

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GROUP	Name of Drug /Extract	Short form used	Dose
Group I	0.9% Normal Saline	NS	0.2ml i.p
Group II	Aspirin (Standard Control)	ASP	150mg/kg i.p
Group III	Aqueous extract of fresh rhizome of Z. officinale	AFZ	100mg/kg i.p
Group IV	Aqueous extract of fresh rhizome of Z. officinale	AFZ	200mg/kg i.p
Group V	Methanolic extract of fresh rhizome of Z. officinale	MFZ	100mg/kg
Group VI	Methanolic extract of fresh rhizome of Z. officinale	MFZ	200mg/kg

Doses were selected as per previous research for anti inflammatory activity of ginger extract.[14] Acute toxicity study was done. No mortality was seen upto 2000mg/kg methanolic extract of zingiber officinale. All experiment were conducted after approval of institutional animal ethics committee. (Certificate No:IAEC/KIMS/2019/09). Experiment were conducted as per CPCSEA guidelines.

Evaluation of anti inflammatory activity

It was done by carrageenan induced paw edema method. [15]

Carrageenan-induced Oedema in rat hind paw

This method is based on the plethysmometeric measurement of oedema produced by sub plantar injection of carrageenan into the hind paw of albino rats. Acute inflammation is produced by sub plantar injection of 0.1 ml of freshly prepared 1% suspension of carrageenan in normal saline in the right hind paw of the rats and paw volume is measured plethysmometrically hourly till the fourth hour after carrageenan injection. Percentage inhibition (protection) against oedema formation is taken as an index of acute anti-inflammatory activity. It is calculated as follows

Percentage Inhibition = (Vc – Vt / Vc) x 100 Where:
Vc = Volume of paw oedema in control animals Vt =
Volume of paw oedema in treated animals.

Statistical analysis

Results were expressed as mean ± standard deviation (SD). Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Dunnett's t-test for post-hoc analysis.

$P < 0.05$ considered statistically significant
All the statistical methods were carried out using the SPSS software.

Results

Table 1
Effect of ASP150, AFZ100, AFZ200, MFZ100, MFZ200 treatments on carrageenan induced paw edema compared with control

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Time after carrageenan injection	Paw edema volume in ml (Mean ± SD)						ANOVA	
	Control	ASP 150	AFZ 100	AFZ 200	MFZ 100	MFZ 200	F value	P Value
1 hr	1.04 ± 0.188	0.41 ± 0.302*	0.45 ± 0.188*	0.25 ± 0.158*	0.16 ± 0.129*	0.12 ± 0.136*	18.327	<0.0001
2 hr	1 ± 0.353	0.33 ± 0.129*	0.45 ± 0.332*	0.37 ± 0.262*	0.20 ± 0.102*	0.33 ± 0.129*	8.150	<0.0001
3 hr	1.08 ± 0.408	0.20 ± 0.188*	0.45 ± 0.188*	0.37 ± 0.209*	0.29 ± 0.102*	0.29 ± 0.188*	11.344	<0.0001

Post hoc analysis by Dunnett's Test: * $p < 0.05$

ANOVA revealed statistically significant difference in study groups; control, ASP150, AFZ100 , AFZ200 , MFZ100 , MFZ 200 .
Post hoc analysis by Dunnett's Test revealed statistically Significant difference between all treatment groups when compared with Control at all time interval (P < 0.05). Bonferroni Multiple Comparison test revealed, no statistically significant difference in anti-inflammatory activity of all extracts compared with Aspirin at 1hr, 2hr, 3hr time interval (P > 0.05).

Graph 1. Effect of ASP150, AFZ100, AFZ200, MFZ100, MFZ200 treatments on carrageenan induced paw edema compared with control

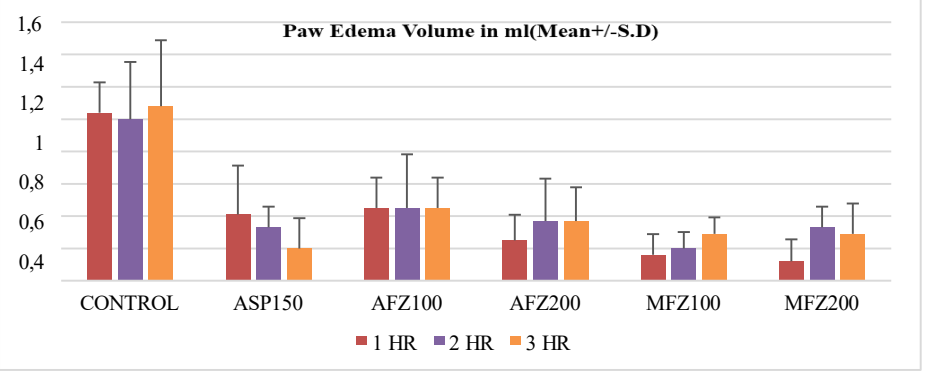

Table 2
Percentage inhibition of paw edema in AFZ100, AFZ200, MFZ100, MFZ200 treatments treated group compared with Aspirin group at different time intervals

Groups	1hr	2hr	3hr
ASP	60 %	67 %	81.48 %
AFZ 100mg/kg	56.73 %	55 %	62.03 %
AFZ 200mg/kg	75 %	63 %	65.7 %
MFZ 100mg/kg	84 %	80 %	73 %
MFZ 200mg/kg	88.46 %	67 %	73.14 %

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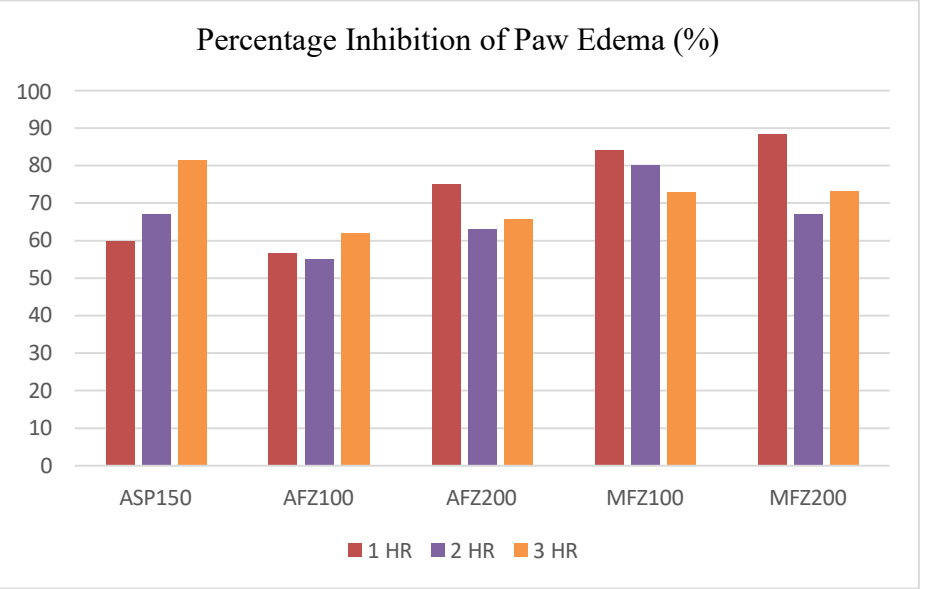

Graph 2. Percentage inhibition of paw edema in AFZ100, AFZ200, MFZ100, MFZ200 treatments treated group compared with Aspirin group at different time intervals

Discussion

The current research examined the anti-inflammatory properties of varying concentrations of fresh rhizome methanolic and aqueous extracts of the Zingiber Officinale plant in animal models of inflammation. We chose to use the Carrageenan-induced paw edema approach for its anti-inflammatory properties. A minimum of 115 components have been found in both fresh and dried ginger. The most important ones among them are gingerols. Shogaols are more prevalent in dry ginger than in fresh, whereas they are more prevalent in fresh ginger and less in dry ginger. They are known as the main dehydration products for gingerol. 16 Ginger may have an anti-inflammatory impact via a variety of ways. Prostaglandin and leukotriene production may be inhibited by ginger 17. Arachidonate 5-lipoxygenase inhibition may also contribute to ginger's anti-inflammatory properties. 18 Gingerol 20 is also said to be the cause of ginger's anti-inflammatory properties by inhibiting proinflammatory cytokines and cyclooxygenase 2 (COX 2).

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Aqueous extract of fresh rhizome (AFZ 100 and AFZ 200)

When compared to the control at one, two, and three hours, we discovered that the aqueous extract of fresh Zingiber Officinale rhizome at doses of 100 mg/kg and 200 mg/kg (AFZ 100 and AFZ 200) significantly reduced the amount of paw edema ($p < 0.05$). At all time intervals, there was no statistically significant difference in the anti-inflammatory activity of aspirin and AFZ 100 or AFZ 200 ($p > 0.05$). It suggests that AFZ 100 and AFZ 200 have anti-inflammatory properties similar to aspirin. At 1-, 2-, and 3-hour intervals, AFZ 100 shown a 56.73%, 55%, and 62.03% reduction in inflammation, whereas AFZ 200 demonstrated a 75%, 63%, and 65.7% reduction in inflammation at 1-, 2-, and 3-hour intervals, respectively. Even though AFZ 100 and aspirin have similar anti-inflammatory properties, AFZ 100's impact is less than aspirin at all time intervals, whereas AFZ 200's is more than aspirin just for one hour. Overall, it was shown that the aqueous extract of fresh Zingiber Officinale rhizome showed dose-dependent increases in anti-inflammatory effect from 100 mg/kg to 200 mg/kg.

Methanolic extract of fresh rhizome (MFZ 100)

We found that methanolic extract of fresh rhizome of plant Zingiber Officinale at a dose of 100mg/kg (MFZ 100) showed statistically significant inhibition of paw edema volume ($p < 0.05$) when compared to control at 1hr, 2hr and 3hr. There was no statistically significant difference in anti-inflammatory activity of aspirin and MFZ 100 at all-time interval ($p > 0.05$). It indicates anti-inflammatory activity of MFZ 100 is comparable to aspirin. MFZ 100 has shown decrease in inflammation by 84%, 80% and 73% at 1hr, 2hr and 3hr interval respectively. Though anti-inflammatory activity of MFZ 100 is comparable to aspirin, it is more than aspirin at 1hr and 2hr interval.

Methanolic extract of fresh rhizome (MFZ 200)

When compared to the control at one, two, and three hours, we discovered that a 200 mg/kg methanolic extract of fresh Zingiber Officinale rhizome (MFZ 200) significantly reduced the amount of paw edema ($p < 0.05$). At all time intervals, there was no statistically significant difference between MFZ 200 and aspirin's anti-inflammatory effect ($p > 0.05$). It shows that MFZ 200's anti-inflammatory properties are on par with aspirin throughout all time periods. At 1-, 2-, and 3-hour intervals, MFZ 200 has shown a reduction in inflammation of 88.46%, 67%, and 73.14%, respectively. At every time point, the MFZ 200-induced percentage suppression of paw edema is the highest of all treatment groups. It was clear from comparing the percentage inhibition of paw edema at all time intervals that the aspirin effect peaked at three hours, whereas the activity of the aqueous and methanolic extracts began early and decreased steadily until then.

Therefore, our findings indicate that Zingiber officinale extracts have anti-inflammatory properties. Aspirin-like anti-inflammatory qualities are present. It will be reasonable to mix ginger extract with aspirin (NSAIDs) for long-term treatments of rheumatoid arthritis, low back pain, senile arthritis, and other conditions given the issues of stomach ulcers and

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hepatotoxicity linked to greater dosages of aspirin and other NSAIDs. Because of its anti-inflammatory properties, ginger could increase the effectiveness of aspirin, so we might be able to lower the dosage. Ginger may lessen the likelihood of aspirin-induced side effects because of its hepatoprotective and digestant qualities. As a result, the combination may have a lengthy half-life, a rapid start, a reduction in stomach intolerance, an additional anti-inflammatory effect, and more. Thus, we suggest that more clinical research be conducted to demonstrate the advantages of using ginger extract and NSAIDs together for chronic arthritic diseases.

Summary and Conclusions

We draw the conclusion that Zingiber officinale extracts have anti-inflammatory qualities based on the results of our experimental investigation. In an animal model of acute inflammation, 100 mg/kg and 200 mg/kg dosages of fresh rhizome aqueous and methanolic extracts exhibit strong anti-inflammatory action in comparison to the control, which is equivalent to aspirin's anti-inflammatory properties. The highest level of anti-inflammatory efficacy among all the extracts and the standard control was shown by a 200 mg/kg methanolic extract of fresh Zingiber officinale rhizome. Both MFZ and AFZ have shown dose-dependent anti-inflammatory properties. According to current research, using ginger may help reduce inflammation in a number of inflammatory disorders. Given the side effects of traditional anti-inflammatory medications like NSAIDs and corticosteroids, this study's demonstration of the anti-inflammatory properties of ginger extracts will be a step toward the development of a new, safe medication that will help patients with pain and inflammation. Given the hepatoprotective and digestant properties of ginger extracts, they might be a useful supplement to aspirin or other NSAID treatments for long-term inflammatory diseases like arthritis. Ginger extracts, both aqueous and methanolic, may be used as anti-inflammatory medicines to treat rheumatoid arthritis and osteoarthritis, two chronic inflammatory diseases. However, more research in a variety of different acute and chronic inflammatory models as well as human studies are required to validate the findings and demonstrate their effectiveness when administered over an extended period of time as a possible anti-inflammatory medication in standard clinical practice.

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