INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

ANTIPYRETIC ACTIVITIES OF THE AQUEOUS AND ETHANOL EXTRACTS OF FLOWER HEADS OF *MATRICARIA RECUTITA* AGAINST YEAST EXTRACT INDUCED PYREXIA MODEL IN MICE

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ARTICLE INFO

Article history
Received 13/03/2017
Available online
31/03/2017

Keywords
Phytomedicines,
Matricaria Recutita,
Chamomile,
Antipyretics.

ABSTRACT

Medicinal plants have always been associated with cultural and traditional believes and knowledge. Traditional Medicine constitutes 75-80% of the world's population, mainly in developing countries, for various primary health care activities due to a better cultural acceptability. Phytomedicines obtained from herbal sources are in great demand as they are able to cure many infectious diseases. Matricaria recutita, an herbaceous plant that belongs to compositae family, locally called as chamomile, is used as wound, ulcer, rheumatic pain and other Aliments treatment including fever in children. The objective of the present study was to evaluate the antipyretic activities of the aqueous and ethanol extracts of flower heads of Matricaria recutita in mice. Qualitative experimental study was done in mice. Rectal temperature was recorded before and after inducing pyrexia as well after administration of the respective extracts every half an hour for three hours. Parallel experiments were conducted with the standard antipyretic (aspirin) and the negative control (distilled water). Both extracts showed significant antipyretic activity at the specified dose levels except for 100mg/kg aqueous extract. The antipyretic activities for both extracts were found to be dose dependent. No significant potency difference was observed for aqueous and ethanol extracts though the effects of aqueous extract were not statistically significant to the end of the experiment. In this pharmacological evaluation, the aqueous and ethanol extracts of dried flower heads from Matricaria recutita were extensively investigated for their antipyretic activities against yeast extract induced pyrexia model in mice. The statistically processed result supports that both extracts possess antipyretic activities. Further studies on the same plant at molecular level, to determine the mechanism of action and particular active ingredient responsible for antipyretic activity were recommended.

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*Please cite this article in press as **Kassahun Dires** et al. Antipyretic Activities of The Aqueous and Ethanol Extracts of Flower Heads of Matricaria Recutita Against Yeast Extract Induced Pyrexia Model in Mice. Indo American Journal of Pharmaceutical Research.2017:7(03).*

INTRODUCTION

Discordes is thought to have been the first physician to have prescribed willow bark extract for clients suffering from rheumatism, while the antipyretic effect of willow bark was reported in detail for the first time in 1763. Willow bark was found to contain salicin, a salicylate compound that was later converted to salicylic acid and aspirin. Aspirin was found to inhibit the cyclo-oxygenase-1 and cyclo-oxygenase-2 pathways and therefore to have potent analgesic and anti- inflammatory effect but associated with a lot of unwanted effects like: risk of gastric bleeding, aggravation of viral infections in children. Selective COX2 inhibitors are not recommended because of heart disorder. Hepatotoxicity is commonly reported from paracetamol. Because of cost and side effects of currently available antipyretic drugs, the pharmaceutical industry has been searching for safe and effective alternatives [1].

Phytomedicines obtained from herbal sources are in great demand as they are able to cure many infectious diseases. These plant based drugs provide outstanding contribution to modern therapeutics. They have proved efficacy and safety for primary health care. They also offer therapeutics for age-related disorders like memory loss, osteoporosis, and immune disorders. The integration of phyto medicine into the health system should be developed in such a way to bring harmony between the traditional and modern system of health care with minimum threat to each other [2].

The febrile response is a complex physiologic reaction to disease involving a cytokine-mediated rise in body temperature, generation of acute-phase reactants and activation of endocrinology and immunologic systems. Understanding the basic mechanisms and underlying phenomenon helps to formulate rational approaches to treatment [3].

Matricaria recutita is an herbaceous plant that belongs to compositae family. This plant is locally called as chemomilla. The use of *Matricaria recutita* as medicinal plant dates back to ancient Greece and Rome. The ancient Egyptians considered the herb as sacred gift from the sun God and used it to alleviate fever and sun stroke [4].

Figure 1: ***Matricaria recutita.***

Some of well documented potential general pharmacological activities of *Matricaria recutita* include Sedative activity [5], Anti-ulcerogenic activity [6]. Antimicrobial activities Anti-cancer activity [7], Anxiolytic agent, Analgesic activity [8].

Although the above findings were well documented about potential general pharmacological activities, the antipyretic activity of flower heads from *Matricaria recutita* is not well investigated and documented. Thus the aim of the present study was, to evaluate the antipyretic activities of the aqueous and ethanol extracts of dried flower heads of chamomile in mice.

MATERIALS AND METHODS

Collection of the plant material

After getting a support letter from Deberebirhan University Research and Community Service Office to Ankober woreda development association and getting permission, the flower heads of *Matricaria recutita* were collected from Ankober (170 kilo meter to the north from Addis Ababa and 40 km from the study area, Deberebirhan University) in October 2015.

Chemicals and Drugs

Chemicals and Drugs used were: Distilled water, Ethanol (70%), powder of acetyl salicylic acid (Barer Schering pharma AG, Germany) and Yeast extract powder (Lot. number0000076357).

Experimental animals

The experiment was performed in house bred albino mice (both sexes weighing 25-35 g) which were obtained from department of pharmacology, school of medicine, Addis Ababa University (AAU). They were kept in cages in animal house with a 12-h- light: 12-h-dark cycle. They fed on pellets and drink clean water adlibitum. Mice were allowed to adapt the experimental room one hour before experiments.

Preparation of the extract

Eight hundred gram of the herbal material was air dried and coarsely powdered. Four hundred gram of the powdered material was macerated with distilled water for 14 days with occasional shaking. The remaining four hundred gram was macerated with ethanol. Both the aqueous and ethanol extracts were filtered. The aqueous extract was placed in deep freeze to solidity. The solidified aqueous extract was placed in lyophilizer machine and a gummy residue with a calculated yield of 2.5% was obtained. The ethanol extract was placed in oven for three days. After the ethanol was removed, it was solidified in freeze and kept in lyophilizer machine so a powder with a yield of 3.7% was obtained. The gummy residue and the powder extracts were properly stored and finally reconstituted in distilled water to get the desired concentration for administration in to mice.

Acute toxicity study

The aqueous and ethanol extracts of *Matricaria recutita* flower heads were studied for acute oral toxicity as per revised Organization for Economic Cooperation and Development (OECD) guidelines No.423 (OECD, 2000).

Antipyretic activity study

Antipyretic activities of both aqueous and ethanol extracts were evaluated by yeast extract induced pyrexia model in mice as described by Navid et al [9]. Mice were fasted over night with water adlib before the experiments. The initial rectal temperature was measured by using digital thermometer. Then pyrexia was induced in all mice by injecting 30%w/v yeast extract powder suspension subcutaneously (10 ml/kg).Sixteen hours after the injection, the rectal temperature of each mouse was measured for the second time. Only mice that showed an increase in temperature of at least 0.5^{o}c and above were used for the experiment. Animals were divided in to eight groups (each containing six animals). Group one served as control (received equal volume of 1ml distilled water); Group two received the standard drug (Aspirin 100 mg/kg). Group three received aqueous extract (100 mg/kg), Group four received aqueous extract (200mg/kg) and last group for aqueous extract received 300mg/kg. The remaining three groups (six, seven and eight) received 100,200 and 300 mg/kg ethanol extracts respectively. Finally, the temperature for each mouse was measured (by inserting digital thermometer about three centimeters in to the rectum of each mouse) at 0.5, 1, 1.5, 2, 2.5 and 3 hours after extracts administration.

Determination of LD50 from the acute toxicity study

The LD50 for both aqueous and ethanol extracts of flower heads from Matricaria recutita was determined as per revised OECD guide line no 423(limit test). A total of twenty mice (both sexes) were used. The highest dose levels (500 and 2000 mg/kg) were reasonably selected for administration in to mice. On the first day of the experiment, mice fasted overnight were given aqueous and ethanol extracts of flower heads of *Matricaria recutita*in a dose of 500mg/kg (five mice for each extract)Then mice were observed for twenty four hours for any lethality. On the next day both aqueous and ethanol extracts were administered orally in to the remaining ten mice (five mice for each extract at a dose of 2000mg/kg). Then mice were observed for twenty four hours.

Statistical analysis

All the values are expressed as mean± standard error of the mean and analyzed for ANOVA and post hoc dunnet's t-test (SPSS version 20).

RESULT AND DISCUSSION

The results are presented in table1 and table2 (Change in body temperature; Time in hour). The Aqueous extract at (200 and 300 mg/kg) also showed a reduction in yeast induced pyrexia whereas the 100mg/kg aqueous extract was not statistically significant for the whole period of the experiment (table1). The ethanol extract of flower heads of Matricaria recutita showed a decrease against yeast induced fever at all doses employed (table2)

This significant difference in antipyretic activities between aqueous and ethanol extracts at 100mg/kg dose level might be due to the difference in the chemical nature of active constituents between the two extracts. Since water is a polar solvent, it is expected to isolated polar components only. Unlike water, ethanol has predominant hydrophilic and some liphophilic properties i.e ethanol is capable of extracting both polar and non polar components from chamomile flower heads [10]. These non- polar constituents of ethanol extract at (100mg/kg) from *Matricaria recutita* flower heads might be responsible for lowering rectal temperature in mice.

The antipyretic activities for both extracts were found to be dose dependent. The antipyretic activities for ethanol extract (at 200 and 300mg/kg dose levels) were comparable with the antipyretic activity of aspirin (100mg/kg). But the lowest dose level of ethanol extract was observed to be less potent than aspirin. The aqueous extract at 200 and 300mg/kg dose levels showed similar degree of antipyretic activity during the initial period of measurement whereas to the end of the experiment aspirin was found to be more potent than aqueous extract at all doses employed. This time dependent antipyretic activity observed for aqueous extract might indicate for the active constituents in aqueous extract to have short duration of action than aspirin.

Time dependent antipyretic activity was also observed for ethanol extract of flower heads from chamomile (decreased with time).This result also provides some clue regarding onset of action for both aqueous and ethanol extracts. Both extracts at specified dose levels (except for 100mg/kg aqueous extract) exhibited antipyretic activity immediately after administration in to mice indicating that both extracts posses rapid onset of action.

Significant potency difference was observed between aqueous and ethanol extracts. The ethanol extract at all doses administered was found to be more potent than the aqueous extract with respect to the corresponding dose levels.

Regarding the duration of action secondary metabolites which are found in ethanol extract might have longer duration of action than those in aqueous extract because significant antipyretic activity was observed for ethanol extract (at high dose levels) long time after administration.

Both aqueous and ethanol extracts possess a significant antipyretic activity which is comparable to the standard antipyretic drug aspirin. Previously, around one hundred active ingredients have been identified in this plant [4]. Among those constituents, the flavonoids were reported to be responsible for most of pharmacological effects [8]. Like the previous reports, the antipyretic activities of this plant might be due to the presence of flavonoids and the probable mechanism for lowering temperature in yeast induced pyrexia may be by decreasing the synthesis of prostaglandins and other mediators secondary to inhibiting the enzymes responsible for prostaglandin production.

The acute oral toxicity study of both aqueous and ethanol extracts of dried flower heads of *Matricaria recutita* was carried out as per OECD guide line number 423 (OECD, 2000). At the end of the study, both extracts were found to be safe in mice when given in large dose up to 2000mg/kg by oral route. The LD50 for both extracts was also determined from the acute toxicity study based on OECD guide line. Based on the guide line mice were initially given 500mg/kg dose then observed for 24 hours for lethality. Since both extracts were safe at 500 mg/kg, the remaining mice were provided with 2000mg/kg aqueous and ethanol extracts and observed for twenty four hours. At the end of the observation, no mouse dead even at 2000 mg/kg indicating that the LD50 for both aqueous and ethanol extracts of *Matricaria recutita* flower heads is greater than 2000mg/kg.

Table1: Effects of oral aqueous extract of dried flower heads of *Matricaria recutita against yeast induced pyrexia* in mice (mean± standard error of the mean) (n=6).

Group	Dose(mg/kg)	T0	TY	0.5HT	1HT	1.5HT	2HT	2.5HT	3HT
Control (Distilled water)	…	36.45± 0.11	37.18± 0.29	37.20± 0.12	37.23± 0.11	37.23± 0.12	37.18± 0.09	37.18± 0.09	37.01± 0.04
Standard (aspirin)	100	36.56± 0.09	37.32± 0.25	36.23± 0.10 (a)	36.20± 0.27(a)	36.30± 0.14(b)	36.20± 0.28(a)	35.26± 0.37(b)	35.50± 0.22(a)
Aqueous	100	36.43± 0.12	37.35± 0.28	36.71± 0.13(n.s)	36.81± 0.15(n.s)	36.91± 0.11(n.s)	36.78± 0.07(n.s)	36.66± 0.14(n.s)	36.61± 0.14(n.s)
Aqueous	200	36.58± 0.13	37.28± 0.30	36.33± 0.15(a)	36.13± 0.26(a)	36.53± 0.10(b)	36.05± 0.23(b)	35.71± 0.26(n.s)	35.81± 0.44(n.s)
Aqueous	300	36.48± 0.15	37.18± 0.29	36.12± 0.24(b)	36.15± 0.27(a)	36.41± 0.15(b)	36.25± 0.27(a)	35.60± 0.51(a)	35.80± 0.28(n.s)

0.5HT, 1HT, 1.5HT, 2HT and 3HT: shows rectal temperature after 0.5, 1, 1.5, 2, and 3 hours of treatment.

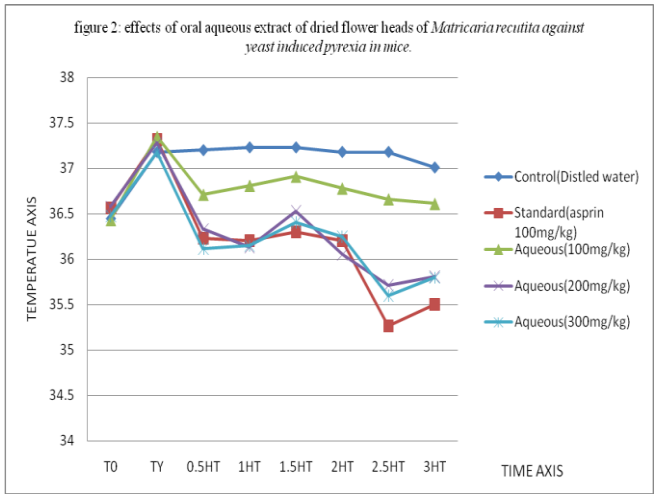
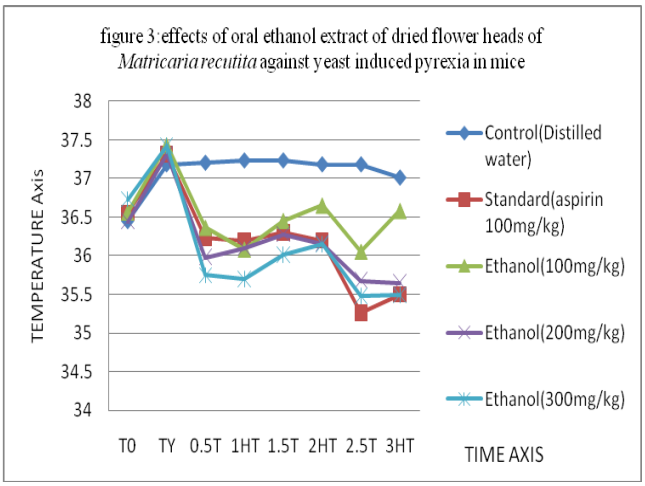


Table2: Effects of oral ethanol extract of dried flower heads of *Matricaria recutita against yeast induced pyrexia* in mice (mean± standard error of the mean) (n=6).

Group	Dose(mg/kg)	T0	TY	0.5T	1HT	1.5T	2HT	2.5T	3HT
Control(Distilled water)	…	36.45± 0.11	37.18± 0.29	37.20± 0.12	37.23± 0.11	37.23± 0.12	37.18± 0.09	37.18± 0.09	37.01± 0.04
Standard (aspirin)	100	36.56± 0.09	37.32± 0.25	36.23± 0.10(a)	36.20± 0.27(a)	36.30± 0.14(b)	36.20± 0.28(a)	35.26± 0.37(b)	35.50± 0.22(a)
Ethanol	100	36.56± 0.14	37.43± 0.26	36.36± 0.18(a)	36.08± 0.25(a)	36.45± 0.19(a)	36.65± 0.06(n.s)	36.05± 0.34(n.s)	36.58± 0.14(n.s)
Ethanol	200	36.45± 0.12	37.32± 0.34	35.98± 0.14(b)	36.10± 0.17(a)	36.28± 0.11(b)	36.16± 0.12(a)	35.68± 0.40(a)	35.65± 0.39(a)
Ethanol	300	36.73± 0.27	37.42± 0.47	35.75± 0.24(b)	35.70± 0.17(b)	36.01± 0.12(b)	36.15± 0.22(a)	35.48± 0.24(a)	35.50± 0.13(a)

0.5HT, 1HT, 1.5HT, 2HT and 3HT: shows rectal temperature after 0.5, 1, 1.5, 2, and 3 hours of treatment
A: significant ($p<0.05$) when compared with the corresponding value of control.
B: extremely significant ($p<0.005$) when compared with the corresponding value of control, Equal volume (1ml).



CONCLUSION

In the present pharmacological evaluation, the aqueous and ethanol extracts of dried flower heads from *Matricaria recutita* were extensively investigated for their antipyretic activities against yeast extract induced pyrexia model in mice. The statistically processed result supports the conclusion that both extracts possess antipyretic activities.

RECOMMENDATION

The statistically processed result showed that both extracts of flower heads from *Matricaria recutita* possess antipyretic activity against yeast extract induced pyrexia in mice. This positive result initiates the need to conduct further studies on the same plant regarding the mechanism of action at molecular level, the particular active ingredient responsible for antipyretic activity and determination of the exact LD50.

ACKNOWLEDGEMENT

The authors wish to acknowledge the financial and over all support of Research and community service office, college of medicine, Debirebirhan University and biomedical Laboratory of Addis Ababa University for their support and cooperation for experimental Animals.

Competing Interests

Authors have declared that no competing interests exist.

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