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Pre-clinical antipyretic herbs: A potential source for modern medicine

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ABSTRACT

Over the past few years natural products have become increasingly popular and the field of natural herbal remedies has flourished to a great extent. Natural herbs have been used for Medicinal purposes for many countries, and continue to be a medicament for various ailments even with the revolution in antibiotics and other synthetic medicine in modern scientific world. Pyrexia or fever is caused as a secondary impact of infection, malignancy or other diseased states. It is the body's natural function to create an environment where infectious agents or damaged tissues cannot survive. It is now clear that most antipyretics work by inhibiting the enzyme cyclooxygenase and reducing the levels of PGE_2 within the hypothalamus. Recently, other mechanisms of action for antipyretic drugs have been suggested, including their ability to reduce pro inflammatory mediators, enhance anti-inflammatory signals at sites of injury, or boost antipyretic messages within the brain. Here we summarized the plants used previously and recently identified for pre-clinical treatment of pyrexia. The present paper is a comprehensive review of different literature sources. The paper discusses the potential of different medicinal plants in curing pyrexia by animal models.

Keywords: Antipyretic activity, Medicinal Plants, Plant extract, Herbal medicine, Rectal temperature

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INTRODUCTION

Plants are important and basic of preventive and curative health care's system since immemorial. Disease is as old as mankind and use of indigenous herbal medicine is a very ancient art and an integral part of treatment[1]. Traditional medicinal herbs have served as a potential source of alternative medicine and different healthcare products. Knowledge of herbal medicines has derived from rich traditions of ancient civilizations and scientific heritage. From ancient time Indian, Chinese, Egyptian, Greek, Roman and Syrian medicinal system documented the use of different plant based medicine for different diseases[2].

According to WHO, nearly 75-80% of world population still depends on herbal medicines. Active constituents from plant sources directly used as therapeutic agent and phytoconstituents are also served as lead molecule for the synthesis of various drugs [2; 3]. Folk medicine and their use against diseases in different cultures is a vast traditional knowledge; which is based on the necessities, instinct, observation, trial and error and long experience of ancient/tribal people[4]. Indigenous or herbal medicines confer considerable economic benefits to most rural and poor people. WHO noted that about 25% of modern medicines are descended from plants sources used traditionally and research on traditional medicinal herbal plant leads discovery of 75% of herbal drugs[3].

Pyrexia:
Pyrexia or fever is caused as a secondary impact of infection, malignancy or other diseased states it is the body's natural function to create an environment where infectious agents or damaged tissues cannot survive .Normal body temperature is regulated by a center in the hypothalamus that ensures a balance between heat loss and production. Fever occurs when there is a disturbance of this hypothalamic 'thermostat', which leads to the set-point of body temperature being raised. Once there has been a return to the normal set point, the temperature regulating mechanisms (dilatation of superficial blood vessels, sweating etc.) then operate to reduce temperature[5]**.** Most of the antipyretic drugs inhibit COX-2 expression to reduce the elevated body temperature by inhibiting PgE_2 biosynthesis[6]**.** Analgesia is the inability to feel pain while still conscious. In view of this, different therapeutic agents are employed like $NSAID_S$, Opioids etc. However, on chronic usage most of these agents produced several side effect including gastrointestinal, renal, hepatic, central nervous system and dermatological effects[7]**.** Therefore, today a large section of world population relies on traditional remedies to treat[8]**.**

Types of fever:
***Continued fever*:** The temperature remains above normal for long period of time.
Intermittent fever: Body temperature periodically rises and falls.
Relapsing fever: Fever that recurs sometimes and number of times, several days after the temperature had returned normal.

ETHANOMEDICINAL PLANTS WITH ANTIPYRETIC ACTIVITY:
***Ficus bengalensis*:**
The antipyretic properties of the various (chloroform, ethanol and water) extract from leaf of *Ficus bengalensis* (Moraceae). Extracts obtained were subjected to evaluate antipyretic activity by yeast induced fevered rats. Aspirin (100 mg/kg) was taken as standard drug. Water and Chloroform extract showed significant decrease in elevated body temperature, while Ethanol extract did not show significant decrease in elevated body temperature as compared to standard drug. It may be concluded that the extracts of leaf of *Ficus bengalensis* showed antipyretic effects,18 h after Yeast injection, chloroform extract (40.09±0.008) $^{\circ}$C, ($P < 0.05$)[9]**.**

***Morinda citrifolia*(Noni):**
The antipyretic activity of aqueous and alcoholic extracts of *Morinda citrifolia*(Noni) fruit on yeast induced pyrexia in rats. The drug was administered orally to a group of rats in graded doses of 250, 500 and 1000 mg/kg body weight. The aqueous extracts of *Morinda citrifolia*(Noni) at doses 500 mg/kg showed a significant decrease in pyretic temperature, the decrease being from 102.73 °F ± 0.09 to 101.21 °F ± 0.02, 100.13 °F ± 0.01 and 100.06 °F ± 0.02 in 2, 3 and 4 h of treatment respectively. Aqueous extracts of *Morinda citrifolia*(Noni) at doses 1000 mg/kg also showed a significant decrease in pyretic temperature, the decrease being from 102.82 °F ±0.05 to 100.47 °F ± 0.09 and 100.07 °F ± 0.01 in 2 and 3 h of treatment respectively. Alcoholic extracts of *Morinda citrifolia*(Noni) at doses 500 mg/kg also showed a significant decrease in pyretic temperature, the decrease being from 102.70 °F ± 0.09 to 100.38 °F ± 0.04 and 100.03 °F ± 0.01 in 2 and 3 h of treatment respectively. Alcoholic extracts of *Morinda citrifolia*(Noni) at doses 1000 mg/kg showed a significant decrease in pyretic temperature from 1 h onwards, the decrease being from 102.76 °F ±0.09 to 101.14 °F ± 0.02, 100.06 °F ± 0.02 and 100.01 °F ± 0.25 in 2, 3 and 4 h of treatment respectively. The significant ($P < 0.01$) difference in antipyretic activity at different time intervals was estimated. Alcoholic and aqueous extracts of *Morinda citrifolia*(Noni) at graded doses showed significant antipyretic action. Both aqueous and alcoholic extracts of *Morinda citrifolia*(Noni) at doses 250 mg/kg did not showed any significant antipyretic activity[10].

Caesalpinia sappan:
The ethanolic extract of the roots of the plant *Caesalpinia sappan* at the 100, 200 and 400 mg/kg was used for the antipyretic activity. *Caesalpinia sappan* ethanolic extract at 400 mg/kg at 1 h showed a significant decrease in pyretic temperature was 38.33±0.076 $^{\circ}$C, ($P<0.01$). The *Caesalpinia sappan* possesses significant antipyretic effect in a yeast-induced elevation of body and it exhibited dose dependent antipyretic activity[11].

***Amaranthus viridis*:**
The methanolic extract of whole plant of *Amaranthus viridis* at the doses of 150, 200 and 400 mg/kg was used for antipyretic activity. *Amaranthus viridis* methanolic extract at 400 mg/kg shows an antipyretic Activity 19 h after the administration of Brewer's yeast up until the end of the experiment, while a 200 mg/kg dose 38.28 ± 0.17 $^{\circ}$C ($P<0.05$) showed a reduction in temperature 22 h the administration of Brewer's yeast and it lasts up to 23 h. The

Amaranthus viridis possesses significant antipyretic effect in a yeast-induced elevation of body temperature in rats and this may be due to an anti-inflammatory effect[12]**.**

Hygrophila spinosa:
The various extracts of *H. spinosa* leaf were used for on Brewer's yeast-induced pyrexia in rats. Chloroform and alcoholic extracts produced significant antipyretic activity but petroleum ether and aqueous extracts did not. Chloroform extract significantly decreased the elevated rectal temperature 3 h after the administration of a dose of 400 mg/kg only 37.61 ± 0.21 °C, ($P<0.05$), while the alcoholic extract reduced the hyperthermia at both 200 and 400 mg/kg doses 1 h after administration. The antipyretic activity of chloroform and alcoholic extracts of *H. spinosa* is probably by inhibition of prostaglandin synthesis in hypothalamus[13].

Pergularia daemia and Carissa carandas:
The ethanol extracts of *P. daemia* 100 mg/kg showed36.13 ± 0.042 °C, the aqueous extracts of *C. carandas*200 mg/kg showed36.86 ±0.021 °C decreases in temperature. Both plants produced significant antipyretic activity in Brewer's yeast induced pyrexia in rats and in this situation both extracts could inhibit the prostaglandins synthesis in hypothalamus. The ethanol and aqueous extracts of *P. daemia and C. carandas*(100 & 200 mg/kg) produced significant antipyretic activity at 60 min. Both plants showed significant ($P<0.01$) antipyretic activity throughout the observation period up to 3h[14].

Tectona grandis:
The methanolic extract of the roots of the plant, *T.grandis* 250 and 500 mg/kg While maximum lowering of body temperature was noticed at 500 mg/kg of the root extract,100.43 ± 0.36 °F,($P<0.05$) within 2 h period in a dose-dependent manner[15].

Chenopodium ambrosioides L:
The aqueous extract of *C. ambrosioides* leaves was used on yeast-induced pyrexia in rats model. A dose dependent antipyretic effect observed with different doses (300-800 mg/kg). The reduction of hyperthermia was pronounced 60 min after administration and was prolonged for three hrs38.38 ± 0.26 °C**,** 37.72 ± 0.33 °C, ($P<0.01$)[16].

Capparis zeylanica:
The effect of methanolic extract of *Capparis zeylanica* plant on yeast induced pyrexia treatment with extracts at dose of 100 mg/kg and 200 mg/kg body weight and paracetamol at dose of 150 mg/kg decreased body temperature of yeast induced rats. At a dose of 200 mg/kg it showed significant antipyretic activity.39.23 ± 0.12 °C, 37.2±0.1°C**,** **(**$P<0.01$). The present results showed that the methanolic extract of *Capparis zeylanica* plant possesses a significant antipyretic effect in yeast induced elevation of body temperature in experimental rats. It was revealed that the extract showed dose dependent antipyretic activity[17].

***Hibiscus sabdariffa calyce*:**
The ethanolic extract *H. sabdariffacalyce* was used on yeast-induced fever in rats. The ethanol extract doses were (400 and 800 mg/kg) used. Both the ethanol of *H. sabdariffacalyces* (800 mg/kg) showed 37.2±0.1 °C and aqueous extract (vacuum dry) of *H. sabdariffacalyces* (800 mg/kg) showed 38.0 ±0.4 °C, ($P<0.05$)decreased the fever induced by yeast in rats. From the result, the ethanol extract showed stronger fever lowering effect than that of the aqueous extract (vacuum dried). Effect of *H. sabdariffacalyces* ethanolic *extract* on yeast-induced fever in rats the ethanol extract (400 and 800 mg/kg) of *H. sabdariffa* significantly reversed yeast induced fever at 2, 4 and 5 h and vacuum dried extract (800 mg/kg) also significantly reduced yeast induced fever at 3, 4 and 5 h after drug administration in rats while the spray dried aqueous extract had no effect on yeast-induced fever. The reference drug aspirin also suppressed fever induced by yeast in rats. Thus, it is possible that more active compound for antipyretic action may be included in the ethanol extract than in the aqueous extract[18].

Cissus quadrangularis:
*Cissusquadrangularis*revealed weak antipyretic effect at low dose i.e. 50 mg/kg b.wt. But at higher dose i.e.100 and 150 mg/kg, 38.68±0.09°C ($P\leq0.01$) it produce marked antipyretic effect in brewer yeast. The various serial extract of the *Cissus quadrangularis* produced a reduction in hyperpyrexia induced by dried yeast injection in rats, with activity being pronounced within 18 h[19].

Platycladus orieantalis:
The antipyretic activity of alcoholic extract of *Platycladus Orieantalis* leaves is probably by inhibition of prostaglandin synthesis in hypothalamus. Extract reduced the hyperthermia at both 200 and 400 mg/kg doses 1 h after administration. Both Paracetamol and alcoholic extract showed significant antipyretic activity throughout the test period of 6 hthroughout the test period of 6 hr. For 200 mg/kg showed 38.15±0.03 °C decrease in temperature(P<0.05)[20].

Cassia occidentalis:
The ethanol and water extracts of *Cassia occidentalis* leaves was used on brewer'syeast-induced pyrexia in rats. Both the ethanol extract and water *Cassia occidentalis* doses 300 mg/kg at 1 h showed decrease in pyretic temperature 39.83±0.15 °C**,** (P<0.05). The doses 300 mg/kg showed significant antipyretic activity at 1 h[21].

Terminalia bellirica:
The ethanolic and aqueous extract of *Terminalia bellirica* fruits was used on Brewer's yeast-induced pyrexia in rats. The Paracetamol as well as ethanolic extract at dose of 200 mg/kg started showing effective antipyretic activity after 1 h of post dosing; while aqueous extract 200 mg/kg reduced temperature after 2 h,37.41 ±0.22 °C,(P<0.05)[22].

Quisqualis indica:
The antipyretic effect of the methanolic extract of leaves of *Quisqualis indica.* The group received methanolic extract 100 mg/kg showed significant decrease in rectal temperature from 38.40±0.075 to 37.44 ± 0.0638 °C and the group received methanolic extract 200 mg/kg showed significant decrease in rectal temperature from 38.99±0.140 to 37.49±0.038 °C respectively as compared with the group received standard drug .And both the dose were found significant to the level of (P<0.01) when compared with that of standard and control group. The methanolic extract of *Quisqualis indica* possesses antipyretic activity more or less depending on the dose levels. The methanolic extract of the plant at a dose level of 100 mg/kg and 200 mg/kg exhibited competent, potent and comparable results promoting *Quisqualis indica Linn*[23].

Borassus flabellifer:
The ethanolic extract of *Borassus flabellifer* male flowers was used on brewer's yeast induced pyrexia in rats. The ethanolic extract of *Borassus flabellifer* 150: at dose 150 mg/kg b.wt. *Borassus flabellifer* 300: at dose 300mg/kg b.wt. showed 36.37± 0.10 °C, **(**P<0.0001) at 1 h.The present results show that *Borassus flabellifer* ethanolic extract possesses a significant antipyretic effect in yeast-provoked elevation of body temperature in rats[24].

Aleurites moluccana:
The methanolic extract of dried leaves of *Aleurites moluccana* was used for anti-pyretic (brewer's yeast induced pyrexia) activity. The anti-pyretic effect of *Aleurites moluccana* methanolic extract (measured as % reduction in body (temperature) was compared with paracetamol (150mg/kg, orally). *Aleurites moluccana* in dose of (300 mg/kg) 67.52±0.75 °C**,**P<0.05.The methanolic extract of *Aleurites moluccana* leaves caused significant decrease in body temperature of rats[25].

Azadirachta indica:
The crude ethanol extract of *Azadirachta indica* leaves was used on yeast-induced pyrexia in rats. The ethanol leaf extract of *A.indica* leaves at 1g/kg and 500 mg/kg was38.12 ± 0.18 °C, significant antipyretic effect (P< 0.05)**.**The ethanol extract of the leaves of *A. indici*a also showed appreciable antipyretic effect (up to 70%) on rats. This effect might be due to inhibition of the synthesis of prostaglandinE2 which is described as key mediator of fever[26].

Anisomeles malabarica:
The various extracts of *Anisomeles malabarica* leaves was used on Brewer's yeast induced pyrexia in albino rat. Oral administration of the extracts Petroleum ether, ethanol and Aqueous extract at the doses of 50, 100 and 200 mg/kg at 4 h 36.16±0.15 °C significantly suppressed the fever and exhibited promising effects over the control in 3 and 4 h. Both paracetamol and extract treated rats were compared with the control group and a significant reduction in the yeast induced elevated rectal temperature was observed, (P<0.05)[27].

Bombax malabaricum:
The methanol extract of *Bombax malabaricum* leaves was used for antipyretic activity in rats. Administration of Baker's yeast produced an increase in the body temperature of the rats. Temperature from normal 37.66 ± 0.02 °C to

38.69 ± 0.03 °C within 4 h of yeast injection was recorded. The temperature was attained in the control group at 1 h (i.e., 5 h after yeast administration) with a value of 39.2 ± 0.04 °C. *Bombax malabaricum* methanolic extract, (200 and 400 mg/kg) and paracetamol reduced the body temperature to 38.17±0.05 °C, 37.97 ± 0.05 °C and 37.91 ± 0.05 °C, respectively after 6 h. *Bombax malabaricum* extract antipyretic activity at doses of 200 mg/kg ($P<0.05$) and 400 mg/kg ($P<0.01$) was higher than that of control. However, the standard drug, paracetamol 150 mg/kg demonstrated the excellent antipyretic activity ($P<0.001$) compared with that of control. After 8 h, body temperature in the *Bombax malabaricum* extract treated groups (200 and 400 mg/kg) remained essentially unchanged at 38.21 ±0.07 and 37.99 ± 0.04 °C, respectively. The present study showed that the methanol extract of *Bombaxmalabaricum* extract possessed significant antipyretic activity in Baker's yeast-induced pyrexia. The maximum antipyretic activity for *Bombax malabaricum* extract occurred at 6 h, subsequently, up to the 8 h, its activity remained largely unchanged. The antipyretic activity of the extract was dose-dependent with the higher dose producing greater activity[28].

Table1 Ethanomedicinal plants with antipyretic activity.

S. No.	Plants Name (Family)	Part used	Extract	Doses
1	*Ficus bengalensis* (Moraceae)	Leaf	Chloroform, ethanol and water	200 mg/kg
2	*Morinda citrifolia* (Rubiaceae)	Fruit	Aqueous and alcoholic	250, 500 and 1000 mg/kg
3	*Caesalpinia sappan* (Fabaceae)	Root	Ethanolic	100, 200 and 400 mg/kg
4	*Amaranthus viridis* **(**Amaranthaceae)	Whole plant	Methanolic	150, 200 and 400 mg/kg
5	*Hygrophila spinosa* **(**Acanthaceae)	Leaf	Methanolic, butanolic	200 and 400 mg/kg
6	*Pergularia daemia and Carissa carandas* **(**Apocyanaceae)	Roots	Ethanolic, aqueous	100 and 200 mg/kg
7	*Tectona grandis* (Verbenaceae)	Roots	Methanolic	100, 250 and 500 mg/kg
8	*Chenopodium ambrosioides* (Chenopodiaceae)	Leaf	Aqueous	100, 300, 500 and 800 mg/kg
9	*Capparisz eylanica* (capparaceae)	Whole plant	Methanolic	100, 150 and 200 mg/kg
10	*Hibiscus sabdariffa calyce*(Malvaceae)	Calyces	Ethanolic	200, 400 and 800 mg/kg
11	*Cissus quadrangularis* (Vitaceae)	Whole plant	Ethanolic	50, 100 and 150 mg/kg
12	*Platycladus orieantalis* (Cupressaceae)	Leaf	Alcoholic	200 and 400 mg/kg
13	*Cassia occidentalis* (Caesalpiniaceae),	Leaf	Ethanolic and water	150 and 300 mg/kg
14	*Terminalia bellirica* (Combrataceae)	Fruit	Ethanolic and aqueous	200 mg/kg
15	*Quisqualis indica* (Combreteceae)	Leaf	Methanolic	100 and 200 mg/kg
16	*Borassus flabellifer* **(**Arecaceae)	Flowers	Alcoholic	150 and 300 mg/kg
17	*Aleurites moluccana* (Euphorbiaceae)	Leaf	Methanol	100, 150, 200 and 300 mg/kg
18	*Azadirachta indica* (Meliaceae)	Leaf	Ethanolic	500, 1000 mg/ kg and 1g/mg
19	*Anisomeles malabaric* (Lamiaceae)	Leaf	Pet. ether, Ethanol and Aqueous	50, 100 and 200 mg/kg
20	*Bombax malabaricum* (Bombacaceae)	Leaf	Methanol	200 and 400 mg/kg

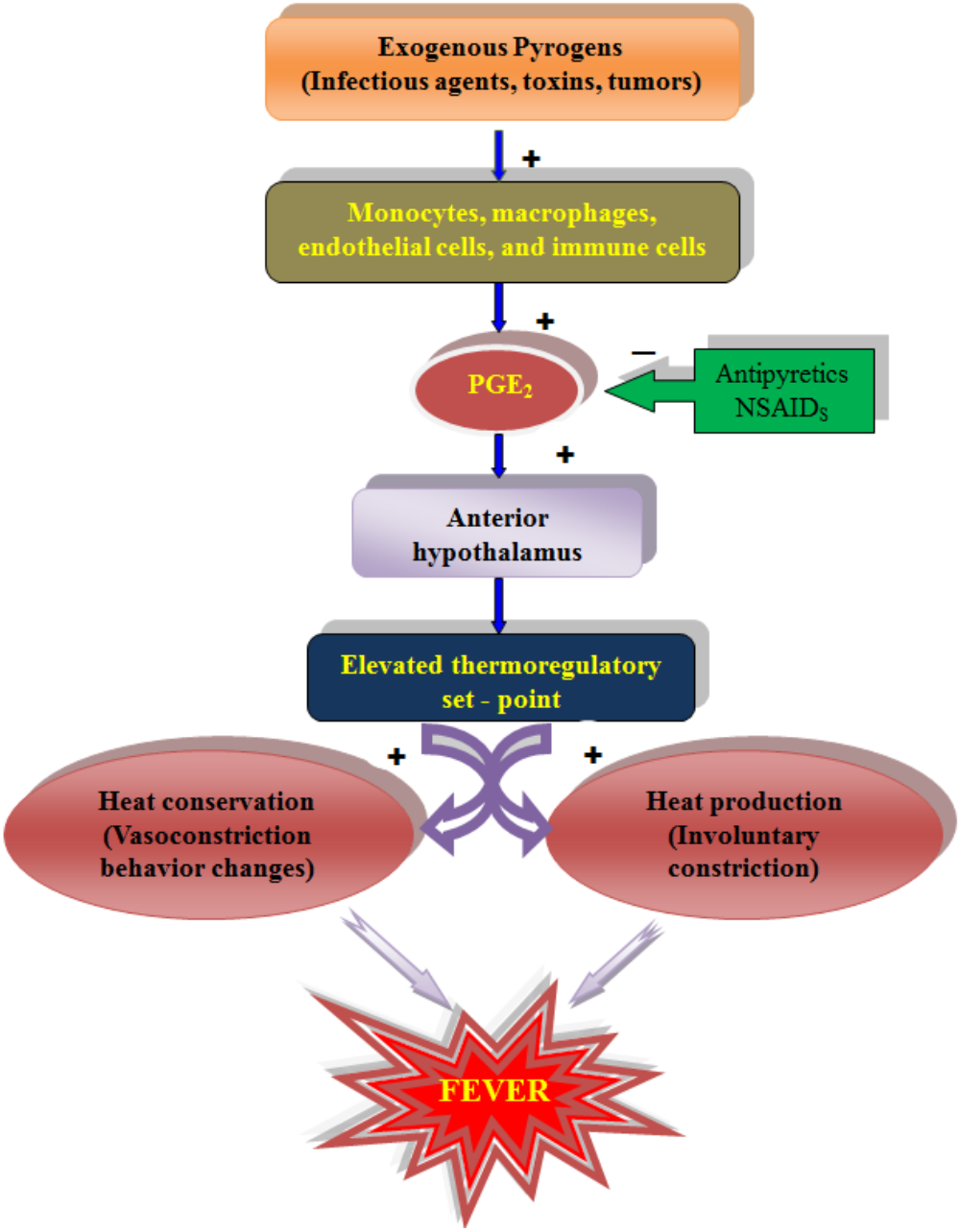

Figure 1: Pathophysiological mechanism of fever

CONCLUSION

The review results suggested that the presence of certain bioactive molecules may partly be responsible for the antipyretic activity. Hence the review study is concluded that the herbal drug possesses antipyretic and it has been proved by animal models which give many links to develop the future trials.

Conflict of interest statement

The authors declare that there are no any conflicts of interest.

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