RECENT ADVANCES IN PHYTOTHERAPY OF PYREXIA

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ABSTRACT Normal body temperature ranges between 37.22°C-40.57°C. Temperature above 40.57°C is considered as pyrexia. Temperature rises due to some disturbances in body's heat regulating mechanism. Toxins (pyrogens) act on white blood cells and produce endogenous pyrogens. These endogenous pyrogens directly act on anterior hypothalamus and in turn lead to increase in the temperature. There are numerous causes of fever such as infections, injury, inflammation, dehydration and certain drugs. In this modern era, most of the medicines made from plants are useful in various ailments. Plants have some active constituents that are involved in treating the disease. People living in developing countries are well known in using these plants for management of pyrexia and 25% people of the developed world also prefer these plants for their medicinal properties. Management of pyrexia has remained a very concerned issuesince early ages and elements derived from the natural medicines have been widely used. Nowadays research inmanagement of pyrexia has enabled us to use natural products in their original form. Purpose of this paper is to review the scientifically proved literature on antipyretic activityof plants.

Key words: Pyrexia, medicinal plants, efficacy

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INTRODUCTION

Pyrexia is a frequent medical symptom that is described as increasing in internal body temperature to a level above the normal, characterized by temperature elevation in body's thermoregulatory set and it occurs when there is a disorder in hypothalamic set point. Fever is produced through the generation of pyrogens which provoke prostaglandin E2. PGE2 proceed on the hypothalamus, which produce reaction on the entire body and results in a new temperature level (1). Increase in body temperature is the response given by human body due to inflammation, tissue damage, cancer and this term is labeled as pyrexia or more commonly fever (2). Ayurveda best describes the beginning of fever as the combination of indigestion, seasonal changes and alternation of daily routine. Children in developing world are exposed to malnutrition and they suffer from fever. This fever also connects with body pain and aches which is the fundamental cause of increase in the disease and death count. There are numerous intermediates which are involved in the pathogenesis of fever. Interleukin-6, tumor necrosis factor and Interleukin-1b are pyrogenic cytokines which are involved in fever by their direct effect on hypothalamus (3). By the stimulation of pyrogenic cytokines, the exogenous pyrogens cause pyrexia (4). Inflammation is a very complex phenomenon which is triggered by any stimulus which can be mechanical injury, burns, infections or any poison which may affect the welfare of anyhost. A type of organic intermediate is arachidonic acid that is transformed into a huge number of eicosanoids with effective natural functions. Cyclooxygenase (COX) pathway is one of the major pathways of arachidonic acid, which is involved in the synthesis of thromboxane and prostaglandins (5). There are many inflammatory diseases in the world which have caused disruption/disability in human and most

common disabling disease is rheumatic disease (6). Researchers are particularly interested in formulating herbal based drugs for treating diabetes, arthritis, hepatitis and incorporating it into national network program. Plants used as medicine are not fully justified as the competition is huge and plenty of other drugs are available which have shown compatible pharmacophores. New pharmacophores need to be developed for targeting drug actions together with that they can be used in combination. One such example is curcumin which is used as target molecules for large number of combination drug regimens (7). Over 75% of the population in the world depends mostly on medicinal plants for the treatment of different ailments. The modern medicines used to treat inflammation and pain exhibit numerous side effects. This guides to significant attention in exploration of safer medicines for these ailments.

Treatment of pyrexia

There are various anti-pyretic drugs which are available to lower the body temperature (8). NSAIDs have anti-pyretic actions. Their action is due to the reserve of cyclooxygenase (COX), an enzyme accountable for the construction of prostaglandins, which are significant mediators of fever. Therefore, NSAIDs are said to possess anti-pyretic properties which rearrange the hypothalamic thermostat and decrease elevated body temperature in fever. NSAIDs increase heat loss by cutaneous vasodilatation and sweating. Paracetamol is widely used as an anti-pyretic agent. Administration of paracetamol generates anti-pyretic action by inhibiting the COX pathway. A major tranquillizer chlorpromazine produces fall in body temperature when administered to humans and animals in an impartial environment. Hypothermic action of chlorpromazine has been used as an adjuvant in production and protection of hypothermia and heat stroke in clinical medicine. Peripheral system for its hypothermic action is adrenoreceptor blockade. It is the natural role of body to generate a condition in which microbes cannot survive. COX-2 expression is decreased by antipyretic drugs to decrease the temperature by slowing down the formation of PgE2 (9). Plants account for several important resources in sustaining the planet (10). Plants are known as the primary producers in all food chains, directly supplying human beings with 90% of their total calorific intake, of which 80% is of proteins. A large number of plants are investigated worldwide for management of pyrexia (Table 1). Medicinal plants possessing antipyretic activity are getting sufficient attention in primary well-being of the individuals (Table 2). Herbal products are considered as safe alternative to modern medicines as they are distinguished as natural (11-13).

***Salix Alba* linn** (Salicaceae)

1. European scientific cooperative on phytotherapy advocate the use of extracts of *Salix Alba* linn for the symptomatic treatment of pyrexia, arthritis and pain. Although the mode of action is not fully understood but its anti-inflammatory effects cannot be denied (14). The actions are only partly attributable to salicylate (15). A hydro-alcoholic extract of willow bark has shown powerful pain killer, anti-inflammatory and antipyretic activity in animals. Extracts of the bark of Salix species had been used for treating fever, mild rheumatic disorders and headache. *Salix alba* contains active constituent salicin, which is the pro-drug of various salicylate derivatives (16). The bark of Salix has anti- inflammatory properties (17). The activity of both aqueous and ethanol extracts of *Achillea millefolium* and *Salix alba* as anti-inflammatory, antipyretics and analgesics are proven. The effects of extracts of both plants on sleeping time were also examined. White willow bark (*Salix alba L*) contains a range of chemical constituents. The salicin is metabolically transformed in the body to the aspirin metabolite, salicylic Salicylates have anti-inflammatory effects in the body. Ethanolic extracts of both *Achillea millefolium* and *Salix alba* could be used as an anti-inflammatory, antipyretic and analgesic agent.

***Trigonella foenum-graecum* L.** (Leguminoseae)
It contains sucrose, D-3-O-methyl- chiroinsitol, ethyl-alpha-D-glucopyranoside, beta-sitosteryl glucopyranoside, stearic acid, glycerol monopalmitate and N,N'-dicarbazyl (18). The leaves were also examined for effective, anti-pyretic and inflammatory actions in the rats (19). Seeds have shown dramatic effects against hyperglycemia and are much safer than clinically available medicines. It is also used as anti-inflammatoryand antipyretic agent (19).

Gongronema latifolium (Asclepiadaceae)
Systematic reviews have identified theanti-diabetic and antioxidant activities of aqueous and ethanol extracts of *G. latifolium* leaves (20). Anti-inflammatory, analgesic and antipyretic drugs are a mixed fraction of compounds, chemically not related;however, share certain beneficial actions. *G.latifolium* contain some active constituentsthat possess anti-pyretic property and hasbeen prescribed in the treatment of pyrexia.

Asparagus racemosus (Liliaceae) *Shatavari*', having many branches, spinouts, the leaves are small and regular, has minute whiteflowers, in small barb and the roots arehandle-likeand bunch (21). It is a straight, sturdily aromaticherb that is widely cultivated in humid regions inIndia. Seeds have been documented for itshypoglycemic activity (25). It contains shatavarin IV,tannin, resin, rutin, quercetin, kaempferol, tyrosine, saponins, sarsasapogenin, isoflavone, curilloside G, oligofurostanosides, asparagamine and racemosol (22). It is very valuable plant and has been used in India for thousands of years and isa well-known stimulant and canbe given to all age groups (23). It is mostly recognized for its many beneficial properties and has several properties like anti-diarrheal anti-depressant, anti-bacterial, anti-ulcer, anti-oxidant and cardioprotective. *Asparagus racemosus* root is an ideal elementof the plant used to treat fever (24).

Achillea millefolium (Asteraceae)
The *Achillea* genus is one of the most important genera in the compound family (26). It contains cosmosiin II, cynaroside I, flavonoids, alkamides, fatty acids, amino acid derivatives, achillicin III, proazulene, lignins, terpenoids, p-hydroxyphenethylamide IV, monoterpenes and sesquiterpenes (27). It is antispasmodic and anti-inflammatory (28-29). This variation can also be found in components of essential oils of *Achillea millefoium.* This plant is used to reduce fever (30-31).

Mollugo pentaphylla Linn (Molluginaceae)
It is used in tumors, scabies, inflammation, eye illness, scurvy, wounds, gout and rheumatism and malaria (32). It is antipyretic, mild laxative, stomachic, antiseptic, emmenagogue, tonic, diuretic, cholagogue, vesicant, rubefacient and malarial fever (33).

Moringa oleifera (Moringaceae)
The root of *Moringa oleifera* possess anti-inflammatory action. It contains phytates, oxalates, saponins, tannins, isothiocyanates, glucosinolates, alkaloids, flavonoids, phenolic acids, polyphenol and carotenoids (34). It isused in pyrexia, epilepsy, inflammation, cancer, hypertension and diabetes mellitus (35). It is antifungal, antibacterial, hepatoprotective, hypoglycemic, antioxidant, hypolipidemic, hypotensive, diuretic, spasmolytic, antiulcer, anti-inflammatory, anti-epileptic, antipyretic, anticancer and stimulant *oleifera* extracts represented antipyretic and wound healing potential in rats (37).

Polygonum glabrum wild (Polygonaceae)
Polygonum glabrum has been used as folk medicine and as component in various Ayurvedic preparations. It contains flavonoids, carbohydrates, glycosides and alkaloids (38-39). Traditionally, it is used in pneumonia, gastric ulcer, jaundice, feverand inflammation (40). It is antispasmodic, astringent, diuretic, rubefacient, vermifuge and anthelmintic (41). A mixture has beenused as a treatment for irritation and stomach pain. The plant decoction has been prescribed in the management of rheumatic arthritis (42)

***Peperomia pellucida* Linn** (Piperaceae).
Various ingredients present in this plant are

reported as anti-neoplastic and antifungal agent (43). It contains methyl ester hexadecanoic acid, 2-naphthalenol and 9,12-octadecadienoic acid (44). It is used in rheumatoid arthritis, renal disorders, headache, gouty arthritis, fatigue, boils, acne, abscesses, abdominal pain, hemorrhage, wounds, hypercholesterolemia, mental disorders, inflammation, depression, pimples, constipation, general weakness, edema, dysuria, hypertension and pyrexia (45).

Salix babylonica (Salicaceae)

Salix babylonica and *Populus nigra* products suggest a possible way to decrease the losses in body development, feed capability and death rate due to heat pressure. It contains terephthalic acid, luteolin-4'-Oglucoside, apigenin-7-O- galactoside, kaempferol-7- O-glucoside, salicin, trichocarpin, salicin and chrysoeriol (46). It is anthelmintic (47). A likely mechanism for the antipyretic activity of *Salixba bylonica* is due to its substance of natural salicylates which has inhibitory potential on prostaglandin synthesis (48). Salicylate has been shown to present little oral toxicity (LD_{50}> 1000 mg/kg) and has been usually renowned as safe (49).

CONCLUSION

Above mentioned discussion has proven the efficacy of medicinal plants in pyrexia. Natural products have always become a subject of international significance over the previous years. Most of the World population still relies on herbal medicine for their health care in developing countries. Medicinal plants have an extensive record of medicinal uses since ancient times. Popularity of medicinal plants for use in different ailments is due to their low cost and fewer side effects as compared to modern medicine. Economic advantages, identification and development of the natural medicines are on the increase in developing countries.

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Table 1: Ethnobotanical distribution of plants for which data from animal experiments exist

Country	Plant name
Pakistan	*Alhagi maurorum, Cymbopogon jwarancusa, Echinops echinatus, Fagonia cretica,Panicum turgidum, Taxus wallichiana* (50).
India	*Capparis zeylanica* (51). *Melia azedarach*, *Cardiospermum halicacabum (52). Alstonia macrophylla, Moringa oleifera* (37). *Tecomaria capensis* (53). *Platycladus orientalis*(54). *Aleuritis moluccana* (55)
Indonesia	*Ceiba pentandra, Gossypium arboretum* (56).
Nigeria	*Gongronema latifolium, Grewia crenata, Striga hermontheca* (57). *Drymaria cordata* (58). *Hunteria umbellata* (59). *Abutilon mauritianum* (60).
Kenya	*Aloe volkensii* (61).
Malaysia	*Thottea dependens* (62).
Saudi Arabia	*Piper cubeba* (63). *Foeniculum vulgare* (64). *Albizia lebbeck* (65).
Bangladesh	*Marsilea trifolia* Blanco (66). *Bambusa vulgaris* (67). *Morinda angustifolia*
China	*Speranskia tuberculata* (68).
Sri Lanka	*Camellia sinensis* (69)
South Africa	*Hippobromus pauciflorus* (70). *Ruta graveolens* (71).
Korea	*Caesalpinia bonducella* (72)

Table 2: Medicinal plants having antipyretic activities							
Plant Name	**Family**	**Parts used**	**Chemical constituents**	**Extraction/dosage form design**	**Dosage**	**Model**	**References**
Cordia dichotoma	Boraginaceae	Leaves	Phenolic contents, flavonoids, alkaloids, saponins, carbohydrates, glycosides	Methanol extract	400 mg/kg	Rats	(73)
Croton zambesicus	Euphorbiaceae	Roots	Isovitexin, apigenin-6-C- glucoside, kaempferol, quercitin, diterpenes	Ethanol extract	27-81mg/kg	Mice	(74)
Momordica charantia	Cucurbitaceae	Fruits	Alkaloids, carbohydrate, tannins, glycosides, proteins, steroids	Ethanolic extracts	250 and 500 mg/kg	Rats	(75)

Cuscuta reflexa	Cuscutaceae	Whole plant	Flavonoids, Saponins, organic acids	Aqueous and ethanolic extracts	200 and 400 mg/kg	Rats	(76)
Bryonia laciniosa	Cucurbitaceae	Leaves	Bryonin, glucomannan, saponin, goniothalamine,punicic acid	Methanol extract	125 and 250 mg/kg	Mice and rats	(77)
Schoenoplectus grossus	Cyperaceae	Roots	Tannins, alkaloids, flavonoids	Methanol extract	400	Mice and rats	(78)
Moringa oleifera	Moringaceae	Bark	Phenolic acid, flavonoids, glucosinolates, thiocyanates, flavonol,kaempferol, quercetin, rutinosides, caffeic acid	Hydro-alcoholic extract	50 and 100 mg/kg	Rats	(79)
Diospyros lotus L.	Ebenaceae	Roots	Lupine triterpenes, dimeric naphthoquinones, naphthalene, sugar,fatty acids, phenolic compounds	Chloroform, ethyl acetate, hexane and butanolfractions	50 and 100 mg/kg	Mice	(80)
Fagonia cretica	Zygophylaceae	Roots	Glycosides, steroids, sterols, coumarins, tannins, saponins, terpenoids, flavonoids, alkaloids	Ethanol extract	500 mg/kg	Rabbits	(81)
Bidens pilosa	Asteraceae	Whole plant	Flavonoids, polyacetylene, terpenoids, sterols, phenylpropanoids	Methanolic extract	500mg/kg	Rabbits	(82)
Cardiospermum halicacabum	Sapindaceae	Whole plant	Xanthoprotein, Tannins, Saponins, Triterpenoids, Steroids,	Ethanol as well n-hexane as extract	400 mg/kg	Rats	(52)

Chloranthus erectus	Chloranthaceae	Leaves	Flavonoids, alkaloids, saponins, glycosides	Methanol extract	100 and mg/kg	Rats	(83)
Tecomaria capensis	Bignoniaceae	Leaves	Alkaloid, phenolic compounds, flavonoids, saponins, glycosides, terpenoids, steroids, coumarins, quinines	Methanol extract	100, 200 and 500 mg/kg	Rats	(53)
Drymaria cordata	Caryophyllaceae	Whole plant	Tannins, phenols, flavonoids, alkaloids, saponins, glycosides	Aqueous extract	100, 200, and 400 mg kg	Mice and rats	(58)
Bauhinia racemosa	Caesalpiniaceae	Stem bark	Flavonoids, tannins, methyl gallate, kaempferol, quercetin	Alcoholic extract	100,200mg/kg	Rats	(84)
Tephrosia pupurea	Fabaceae	Whole plant	flavones, flavanones, prenylated flavonoids, chalcones and rotenoids	Methanolicextract	250 and 500 mg/kg	Rats	(85)
Bombax Malabaricum	Bombacaceae	Leaves	Steroids, carbohydrates,tannins, flavonoids, triterpenoids, deoxy-sugars and coumarin glycosides.	Methanolic extract	200 and mg/kg	Rats	(86)
Bergenia ligulata	Saxifragaceae	Roots, rhizomes & leaves	Steroids, alkaloids, Flavonoids and terpenoids	Ethanolic extract	300 & 500 mg/kg	Rats	(87)
Cynanchum Viminale	Asclepiadaceae	Stem	Flavonoids, saponins, tannins, glycosides, alkaloids	Aqueous extract	150 mg/kg	Mice	(61)

			Steroids				
Cassia occidentalis	Caesalpiniaceae	Leaves	Sennoside,	Ethanolic extract and water extract	150 300 and mg/kg	Rats	(88)
Stachytarpheta indica	Verbenaceae	Stem bark	Saponins,	Methanolicextract	50,100 and 150 mg/kg	Mice	(58)
Acacia jacquemontii	Fabaceae	Rootbark	Tannins, cardioactive glycosides, saponins and flavonoids	Methanolicextract	50 andmg/ 100 kg	Mice	(89)
Solanum melongena	Solanaceae	Leaves	Flavonoids, alkaloids, tannins and steroids	Dry residues	100, 250 and 500 mg/kg	Rats	(90)

Drynaria Quercifolia	Polypodiaceae	Rhizome	Steroids, tannins, and flavonoids	Petroleum ether and ethylacetate soluble fractions of ethanol extract	80 mg/kg	Rabbits	(91)
Carissa edulis	Apocynacea	Leaves, roots and bark	Alkaloids, flavonoids, steroids, phenolics and Terpenoids	Methanolicextract	50, 100 and 150mg/kg.	Rats	(92)
Ocimum gratissium	Labiatae	Leaves	Tannins, flavonoids, saponins, steroid, alkaloids, cardiac glycosides, terpernoids and Phenols	Methanolicextract	100, 200 and 300 mg/kg	Rats	(93)
Azima tetracantha	Salvadoraceae	Leaves	Alkaloids, flavonoids, glycosides,β-sitosterol,	Ethanolicextract	100 and 200mg/kg	Rats	(94-101)

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			tannins, terpenes, protein and coumarin				
Mentha spicata	Labiatae	Whole plant	Carvone and Limonene	Methanolic extract	250 and 500mg/kg	Mice	(95-101)