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Archives of Applied Science Research, 2010, 2 (3): 188-195

(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-508X
CODEN (USA) AASRC9

Medicinal Plants as a Source of Anti-Pyretic Agents – A Review

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Abstract

Fever is a complex physiologic response triggered by infectious or aseptic stimuli. Elevations in body temperature occur when concentrations of prostaglandin E2 (PGE2) increase within certain areas of the brain. These elevations alter the firing rate of neurons that control thermoregulation in the hypothalamus. Although fever benefits the nonspecific immune response to invading microorganisms, it is also viewed as a source of discomfort and is commonly suppressed with antipyretic medication. Antipyretics such as aspirin have been widely used since the late 19th century, but the mechanisms by which they relieve fever have only been characterized in the last few decades. It is now clear that most antipyretics work by inhibiting the enzyme cyclooxygenase and reducing the levels of PGE2 within the hypothalamus. Various medicinal plants are used as an antipyretic agent from the ancient time. In this review we have enlisted around 50 medicinal plants which are used as an antipyretic agent which can be one of the good alternatives for the traditional allopathic antipyretic agents.

Key words: Antipyretic, Fever, Cyclooxygenase, Medicinal plants.

INTRODUCTION

This bon mot from Osler cleverly paints the pall of apprehension felt by those who attend febrile patients at the bedside. Practitioners still debate the role or value of fever in disease, and even iatrogenic pyrexia undergoes periodic revival (1). As victor or villain, perhaps no symptom has been viewed so dichotomously. Fever today is generally regarded as a form of patient discomfort. Among acts of caring, pyrexia is treatable, and so it often is treated. Physicians since antiquity have used various physical means to lower body temperature (2). Applying Peruvian cinchona bark as an antipyretic dates to the early 1600s (3), but by the 18th century over harvesting of cinchona created scarcity (4) and a search for substitutes. In 1763, Reverend Stone reported to the Royal Society of London on the antipyretic effects of “fever bark” from English willow (4). Although his finding appeared novel, it simply confirmed what was known to

Hippocrates, Galen, and ancient Egyptians centuries before (5,6). Salicylic acid was first prepared in 1838 from the glucoside salicin, the active component in willow bark (5,7). Another derivative, acetylsalicylic acid (aspirin) was later synthesized in 1853 and made commercially available as an antipyretic in 1899 (2,5). Since then, numerous antipyretics have been introduced into clinical medicine.

The prescription of acetaminophen for fever is more recent. Although precursors such as acetanilide and phenacetine were developed in the second half of the 19^{th} century, the popular use of acetaminophen as an antipyretic and analgesic did not occur until the 1950s (8). The antipyretics in common use today include acetaminophen, aspirin, and other nonsteroidal anti-inflammatory drugs (NSAIDs). The principal action of antipyretics rests in their ability to inhibit the enzyme cyclooxygenase (COX) and interrupt the synthesis of inflammatory prostaglandins (9). Recent studies on the mechanism of antipyretic action of these drugs, however, reveal effects independent of COX inhibition as well.

Pyrexia or fever is caused as a secondary impact of infection, tissue damage, inflammation, graft rejection, malignancy or other diseased states. It is the body's natural defense to create an environment where infectious agent or damaged tissue cannot survive. Normally the infected or damaged tissue initiates the enhanced formation of pro-inflammatory mediator's (cytokines like interleukin 1β, α, β and TNF-α), which increase the synthesis of prostaglandin E2 (PGE2) near preoptic hypothalamus area and thereby triggering the hypothalamus to elevate the body temperature (10).

As the temperature regulatory system is governed by a nervous feedback mechanism, so when body temperature becomes very high, it dilate the blood vessels and increase sweating to reduce the temperature; but when the body temperature becomes very low hypothalamus protect the internal temperature by vasoconstriction. High fever often increases faster disease progression by increasing tissue catabolism, dehydration, and existing complaints, as found in HIV, when fever during seroconversion results faster disease progression (11). Most of the antipyretic drugs inhibit COX-2 expression to reduce the elevated body temperature by inhibiting PGE2 biosynthesis (12). Moreover, these synthetic agents irreversibly inhibit COX-2 with high selectivity but are toxic to the hepatic cells, glomeruli, cortex of brain and heart muscles, whereas natural COX-2 inhibitors have lower selectivity with fewer side effects (12). A natural antipyretic agent with reduced or no toxicity is therefore, essential.

The pathogenesis of fever

Many of the mediators underlying pyrexia have been described in recent years (Figure 1). The critical “endogenous pyrogens” involved in producing a highly regulated inflammatory response to tissue injury and infections are polypeptide cytokines. Pyrogenic cytokines, such as interleukin-1b (IL-1b), tumor necrosis factor (TNF), and interleukin-6 (IL-6), are those that act directly on the hypothalamus to effect a fever response (13). Exogenous pyrogens, such as microbial surface components, evoke pyrexia most commonly through the stimulation of pyrogenic cytokines. The gram-negative bacterial outer membrane lipopolysaccharide (endotoxin), however, is capable of functioning at the level of the hypothalamus, in much the same way as IL-1b (14).

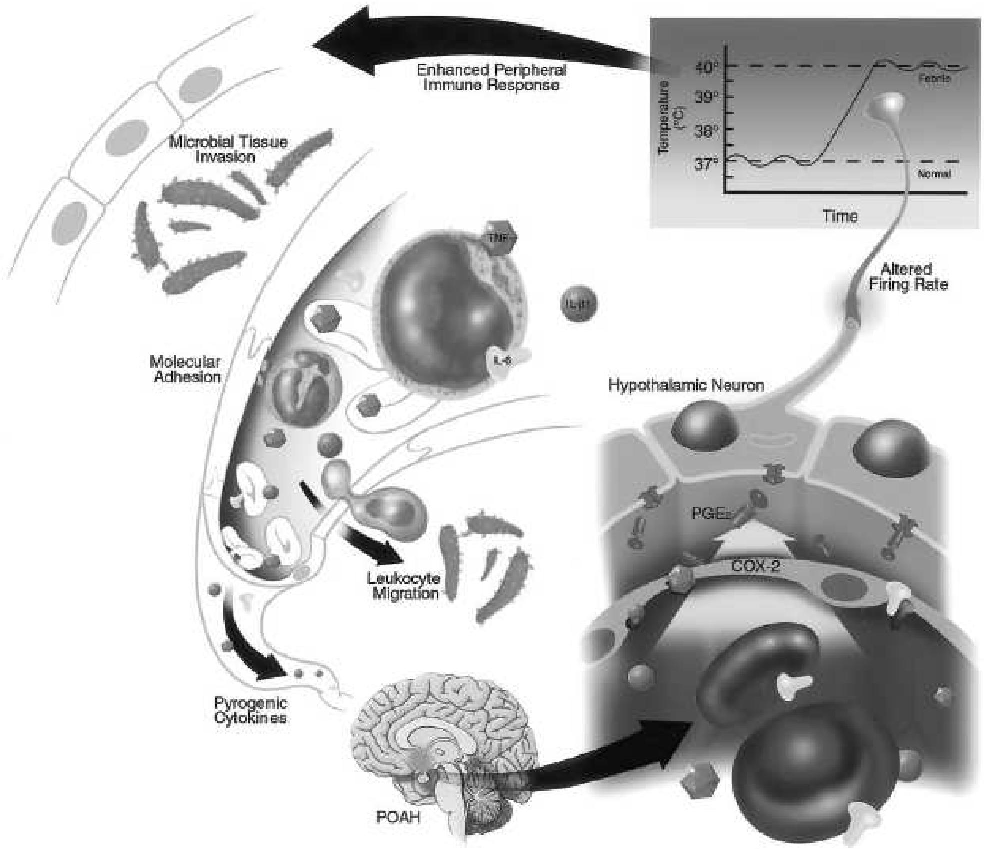

Figure 1: Fever generation after infection. Microbial tissue invasion sparks an inflammatory response and activates local vascular endothelial cells and leukocytes. The extravasation of white blood cells into inflamed areas depends on a multistep interaction with endothelial cells regulated by a variety of cytokines, chemokines, and adhesion molecules. Activated leukocytes release the pyrogenic cytokines interleukin-1b (IL-1b), tumor necrosis factor (TNF), and interleukin-6 (IL-6). Hematogenous dissemination (depicted here) allows these endogenous pyrogens to stimulate vascular endothelial cell production of prostaglandin E2 (PGE2) within the central nervous system. Peripheral inflammatory signals may also travel along neural connections (such as the vagus nerve) to trigger central nervous system PGE2 production. Neurons within the preoptic area of the anterior hypothalamus (POAH) bearing specific E-prostanoid receptors orchestrate the febrile response after the PGE2 signal. PGE2 alters the firing rate of these neurons, resulting in an elevated thermoregulatory set point. The febrile set point body temperature is reached through the regulated evocation of behavioral and physiologic changes aimed at enhancing heat production and reducing heat dissipation. Fever is believed to augment the peripheral and systemic inflammatory response to infection in part by modulating the expression of inflammatory cytokines and enhancing leukocyte function.

These signals trigger the release of other mediators, most notably prostaglandin E2 (PGE2), in the region of the POAH (12). PGE2 is believed to be the proximal mediator of the febrile response. Preoptic neurons bearing E-prostanoid receptors alter their intrinsic firing rate in response to PGE2, evoking an elevation in the thermoregulatory set point. There are four known cellular receptors for PGE2: EP1 through EP4 (15). The particular receptor subtype involved in pyrogenesis is unknown. Although mice lacking the neuronal PGE2 receptor subtype EP3 demonstrate an impaired febrile response to both exogenous (endotoxin) and endogenous pyrogens (15), studies in rats appear to implicate the EP4 receptor (16). The intracellular events triggering pyrexia after PGE2-EP receptor coupling among species are unclear. Fever is tightly regulated by the immune response. Inflammatory stimuli triggering the generation of propyretic messages provoke the release of endogenous antipyretic substances (17). Substances such as arginine vasopressin (AVP), a-melanocyte stimulating hormone, and glucocorticoids act both centrally and peripherally to limit pyrexia (17). The cytokine interleukin-10 (IL-10) has numerous anti-inflammatory properties, including fever suppression (18,19). In addition, a class of lipid compounds known as epoxyeicosanoids generated by certain cytochrome P-450 enzymes plays an important role in limiting the fever and inflammation (20, 21). Analogous to a biochemical feedback pathway, fever itself appears capable of countering the release of pyrogenic cytokines (22,23). For example, febrile temperatures augment early TNF release in endotoxin-challenged mice, yet limit its prolonged (and perhaps detrimental) expression after either lipopolysaccharide injection or bacterial infection (22,23).

Herbs used as anti-pyretic agents

The various plants used as an antipyretic agent are listed in table 1.

Table 1: List of plants used as an antipyretic agents

Sr. No.	Name of the plant	Family	Part used	Reference
1.	*Acanthus montanus*	Acanthaceae	Leaves	24
2.	*Adansonia digitata*	Bombacaceae	Fruit pulp	25
3.	*Aegle marmelos*	Rutaceae	Leaves	26
4.	*Ailanthus excelsa*	Simaroubiaceae	Leaves	27
5.	*Aleurites moluccana*	Euphorbiaceae	Leaves	28
6.	*Alstonia macrophylla*	Apocynaceae	Leaves	29
7.	*Andrographis elongata*	Acanthaceae	Leaves	30
8.	*Andrographis paniculata*	Acanthaceae	Leaves	30
9.	*Araucaria bidwillii*	Araucariceae	Oleo-resin	27
10.	*Bauhinia racemosa*	Caesalpiniaceae	Stem bark	31
11.	*Berberis species*	Berberidaceae	Roots	32
12.	*Borassus flabellifer*	Arecaceae	male flowers (inflorescences)	33
13.	*Caesalpinia bonducella*	Caesalpiniaceae	Seed oil	34
14.	*Capparis zeylanica*	Capparaceae	Whole plant and leaves	35,36
15.	*Centaurea solstitialis*	Asteraceae	Roots and aerial	37

			parts	
16.	*Chenopodium ambrosioides*	Chenopodiaceae	Leaves	38
17.	*Chromolaena odorata*	Asteraceae	Leaves	39
18.	*Cissus quadrangularis*	Vitaceae	Whole plant	40
19.	*Clematis vitalba*	Ranunculaceae	Aerial parts	41
20.	*Cleome rutidosperma*	Capparidaceae	Aerial parts	42
21.	*Cleome viscosa*	Capparidaceae	Entire plant	43
22.	*Clerodendrum petasites*	Verbenaceae	Entire plant	44
23.	*Clitoria ternatea*	Fabaceae	Root	45
24.	*Curcuma longa*	Zingiberceae	Rhizome	46
25.	*Dalbergia sissoo*	Fabaceae	Leaves	47
26.	*Diospyros variegata*	Ebenaceae	Stem	48
27.	*Dodonaea angustifolia*	Compositae	Leaves	49
28.	*Garcinia hanburyi*	Guttiferae	Gamboge from the bark	50
29.	*Hibiscus sabdariffa*	Malvaceae	Red calyces	51
30.	*Hyoscyamus niger*	Solanaceae	Seeds	52
31.	*Isatis indigotica*	Cruciferae	Roots	53
32.	*Laportea crenulata*	Urticaceae	Roots	54
33.	*Lippia multiflora*	Verbenaceae	Essential oil	55
34.	*Magnolia ovata*	Magnoliaceae	Trunk bark	56
35.	*Mallotus peltatus*	Euphorbiaceae	Leaves	57
36.	*Melicope lunu-ankenda*	Rutaceae	Volatile oil	58
37.	*Nelumbo nucifera*	Nymphaeaceae	Rhizomes	59
38.	*Ocimum lamiifolium*	Labiatae	Leaves	60
39.	*Ocimum suave*	Labiatae	Leaves	60
40.	*Parquetina nigrescens*	Periplocaceae	Leaves	61
41.	*Peperomia pellucida*	Piperaceae	Leaves	62
42.	*Phrygilanthus acutifolius*	Loranthaceae	Flowers	63
43.	*Psoralea glandulosa*	Papilionaceae	Aerial part	64
44.	*Salvia africana-lutea*	Labiatae	Leaves	49
45.	*Solanum melongena*	Solanaceae	Leaves	65
46.	*Sphaeranthus indicus*	Compositae	Whole plant	66
47.	*Taxus wallichiana*	Taxaceae	Leaves	67
48.	*Toddalia asiatica*	Rutaceae	Whole plant with root	27
49.	*Trigonella foenum-graecum*	Fabaceae	Leaves	68
50.	*Vernonia cinerea*	Asteraceae	Leaves	69

CONCLUSION

Search for herbal remedies with potent antipyretic activity received momentum recently as the available antipyretics, such as paracetamol, nimusulide etc. have toxic effect to the various organs of the body. The body's ability to maintain a natural balance of COX 1 and 2 that regulate inflammatory response play a crucial role in supporting cardiovascular, immune, neurological, and joint and connective tissue systems. A number of plant extracts modulate enzymes of cyclooxygenase pathway, as reported with the rosmarinic acid of *Rosmarinus officinalis* that inhibit leukotriene and prostaglandins synthesis, while COX-1 and COX-2 was inhibited by cirsilineol, cirsimaritin, apigenin, rosmarinic acid and eugenol of *Ocimum sanctum* similar to ibuprofen, naproxen, and aspirin.

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