MS.ID-IJPBS-2692
International Journal of Pharmacy and Biological Sciences-IJPBS™ (2025) 15 (2): 100-106
Online ISSN: 2230-7605, Print ISSN: 2321-3272
Review Article | Pharmaceutical Sciences | OA Journal | MCI Approved | Index Copernicus

Antipyretic Activity-A Review

V. Asha Jyothi* and Meher Zoya. S

Department of Pharmacology, Shadan Womens College of Pharmacy, Khairatabad, Hyderabad

Received: 22 Jan 2025 / Accepted: 12 Mar 2025/ Published online: 01 April 2025
***Corresponding Author Email:** ashajyothivadlapudi@gmail.com

Abstract
Human beings suffer from many ailments some common and some uncommon. Some ailments last for a short duration while others last for a longer time, one such medical condition is fever. Though fever is taken lightly not all fevers are easily recoverable. Depending on the severity of the medical condition the patient might require rest or might need medical help. In the present publication, the main focus is to study in detail various aspects of antipyretic activity.

Keywords
Antipyretic activity, Pyresis, Fever, Herbal medication, Antipyretic drugs.

*****

INTRODUCTION:
Fever is a medical sign characterized by elevated body temperature above normal (36.5–37.5 °C /98–100 °F) due to an increase in temperature regulatory set point. It is a way of dissipating heat from the body to help regulate body temperature[1].

TYPES:
Performance of the various types of fever
a) Fever continues
b) Fever continues to abrupt onset and remission
c) Fever remittent
d) Intermittent fever
e) Undulant fever
f) Relapsing fever

The pattern of temperature changes may occasionally hint at the diagnosis:

Continuous fever:
Temperature remains above normal throughout the day and does not fluctuate more than 1 °C in 24 hours, e.g., lobar pneumonia, typhoid, urinary tract infection, brucellosis, or typhus.

Intermittent fever:
The temperature elevation is present only for a certain period, later cycling back to normal, e.g. malaria or septicemia.
Following are its types

- Quotidian fever, with a periodicity of 24 hours, typical of Plasmodium falciparum or Plasmodium knowlesi malaria.
- Tertian fever (48-hour periodicity), typical of Plasmodium vivax or Plasmodium ovale malaria.
- Quartan fever (72-hour periodicity), typical of Plasmodium malariae malaria.

Remittent fever:
Temperature remains above normal throughout the day and fluctuates more than 1 °C in 24 hours, *e.g.*, infective endocarditis.

Pel-Ebstein fever:
A specific kind of fever associated with Hodgkin's lymphoma, being high for one week and low for the next week and so on.

A **neutropenic fever,** also called febrile neutropenia, is a fever in the absence of normal immune system function. Because of the lack of infection-fighting neutrophils, a bacterial infection can spread rapidly.

Febricula is an old term for a low-grade fever, especially if the cause is unknown, no other symptoms are present, and the patient recovers fully in less than a week[2].

BENEFICIAL EFFECTS:
In theory, fever can aid in host defense. There are certainly some important immunological reactions that are speeded up by temperature.
Research has demonstrated that fever assists the healing process in several important ways:

- Increased mobility of leukocytes
- Enhanced leukocytes phagocytosis
- Endotoxin effects decreased
- Increased proliferation of T cells[4]

PHYSIOLOGY OF THERMOREGULATION:
Body maintains constant temperature when heat production equals heat loss. This homoeostasis of body temperature is maintained by hypothalamic thermostat. A center for control mechanisms of heat production and heat loss is present in the pre-optic area of hypothalamus. This receives input signals from Thermoreceptors[5,6].

Types of Thermoreceptors:
Thermoreceptors can be classified into:

- Peripheral Thermoreceptors (present in skin and mucous membranes)
- Central Thermoreceptors (present in internal structures such as hypothalamus).

Maintenance of normal body temperature by pre-optic area of hypothalamus (which acts as thermostat) occurs due to either increase or decrease in the firing of nerve impulses with increased and decreased temperature respectively. Hypothalamus contains heat-losing center (predominantly innervated by parasympathetic system) and heat-promoting center (predominantly innervated by sympathetic system)[7,15].

MECHANISMS OF HEAT PRODUCTION[5]:
Different mechanisms of heat production in body include:
Vasoconstriction: Vasoconstriction occurs due to sympathetic nerve stimulation lading to decreased flow of warm blood from internal organs to skin. Hence this leads to increase in body temperature.
Sympathetic stimulation: Stimulation of sympathetic system leads to secretion of epinephrine and norepinephrine (NE) which increases the cellular metabolism. This leads to increased heat production by the process of chemical thermogenesis.
Skeletal muscles: Increase in the muscle tone of skeletal muscles causes shivering by a process of involuntary thermogenesis.
Thyroid hormones: Cold environment leads to increased secretion of TRH by hypothalamus which leads to increased TSH production by pituitary gland. This causes increased production of thyroid hormones (T3 and T4) leading to increase in metabolic rate and inturn body temperature.

MECHANISMS OF HEAT LOSS[5]:
Heat loss through the body occurs by vasodilatation; decreased metabolic rate and shivering or by increased perspiration which usually occurs by stimulation of sweat glands.

PATHOPHYSIOLOGY OF FEVER [6,8]:
A substance which induces fever is called a "pyrogen". Pyrogens can be:
Endogenous pyrogens: These are internal in nature. These include cytokines such as interleukins-1,6,8; tumour necrosis factor-α, β; interferons –α, β. These are produced by phagocytic cells and are released circulation. These then cross BBB enter the brain and bind with endothelial receptors leading to activation of arachidonic acid pathway, release of PGE2 and fever.
Exogenous pyrogens:
These are external in nature. These include lipopolysaccharides (LPS) which are usually the components of cell walls of bacteria.
These LPS bind to LPS binding site to form a complex which binds to CD14 receptors present on macrophages. This causes synthesis and release of endogenous cytokines like IL-1,6; TNF-α, β; and in turn activation of arachidonic acid pathway, PGE2 release and fever production[7].

MECHANISM OF FEVER PRODUCTION:
Pyrexia can be due to infectious toxins or immune responses. These trigger the release of cytokines IL-1, 6; TNF which either act on Thermoreceptors to produce PGE2 in hypothalamus or EP3 receptors in vasomotor center which are also acted upon n by PGE2. This leads to stimulation of sympathetic nerves and increased heat
Production by thermogenesis or decreased heat loss by skin vasoconstriction. This leads to production of fever by decreased heat dissipation. The new set point in hypothalamus remains elevated until PGE2 is no longer present[8].

ANTIPYRETIC THERAPY:
CLASSIFICATION OF ANTIPYRETIC DRUGS[10,11]:

I. Salicylates: Ex: aspirin, diflunisal
II. P-amino phenol derivatives: Ex: paracetamol
III. Pyrazolon derivatives: Ex: phenylbutazone, oxyphenbutazone
IV. Benzoxazocaine derivatives: Ex: piroxicam, meloxicam
V. Propionic acid derivatives: Ex: ibupfen, ketoprofen

VI. Selective COX-2 inhibitors: Ex: celecoxib, paracoxib

HOME REMEDIES FOR FEVER:

Physical cooling methods such as sponging with luke warm or cold water, drinking lots of fluids and water help in controlling fever by decreasing the body temperature[10].
(Massachusetts Department of Public Health
Flu: What You Can Do – Caring for People at Home
Fever and the Flu
Fall 2007)

PRECLINICAL PERSPECTIVE:

Animal models for pyrexia are important biological tools to understand basic processes development of fever and validate strategies for clinical treatment. In general, animal models (with the exception of some transgenic and targeted gene deletions) attempt to reflect human pyrexia[13]. Often practical issues, such as cost, availability, housing costs, and animal husbandry, dictate the choice of animal model.

MODELS TO INDUCE PYREXIA[14]:

IN RATS: Brewer's yeast induced pyrexia: The subcutaneous injection of Brewer's yeast suspension produces fever in rats. Then the animals are treated orally with standard drug and test compound. The maximum reduction in rectal temperatures is calculated between different groups.

IN RABBITS: Lipopolysaccharide induced pyrexia: Intravenous injection of lipopolysaccharides induces fever in rabbits. Test compound is given subcutaneously or orally and decrease in body temperature is compared before administration of the test compound, which is monitored for atleast 3 hours.

Table-II: PREVIOUS WORK DONE ON PLANTS:

S. No.	PLANT NAME	FAMILY	PLANT PART USED	ANIMALS USED	METHOD OF EXTRACTION	SCREENING MODEL	P-VALUE	YEAR
1	Eugenol	Myrtaceae	Clove oil	Rabbits	Saline suspension	IL-1 induced fever	<0.01	Feng et al, 1987[39]
2	Andrographis alata	Acanthaceae	Whole plant	Male wistar rats	Alcoholic extracts	Brewer's yeast induced pyrexia	<0.05	S.Balu et al, 1993[20]
3	Clerodendron serratum	Verbanaceae	Roots	Mice/rats/rabbits	Ethanolic extract	Method of brownlee	<0.05	N.Narayanan et al, 1999[41]
4	Premna herbaceae	Verbanaceae	Roots	Mice/rats/rabbits	Ethanolic extract	Method of brownlee in rabbits	<0.01	N.Narayanan et al, 2000[40]
5	Mallotus peltatus	Euphorbiaceae	Leaves	Wistar rats	Methanolic extract	Brewer's yeast induced pyrexia	<0.001	D.Chatopadhyay et al, 2002[46]
6	Pergularia extensa	Asclepediaceae	Leaves	Wistar rats	Ethanolic	Brewer's yeast induced pyrexia	<0.001	Jalalpure et al, 2002[30]
7	Tabernaemontana pandacaqui	Apocyanaceae	Stems	Sprague dawley rats	Ethanolic extract	Brewer's yeast induced pyrexia	<0.05	T.Taesotikul et al, 2003[45]
8	Alstonia macrophylla	Apocyanaceae	Leaves	Wistar rats	Methanolic extraction	Brewer's yeast induced pyrexia	<0.001	Debprasad chatopadhyay et al, 2005[18]
9	Moringa oleifera	Moringaceae	Seeds	Male wistar rats	Ethanolic, petroleum ether extracts	Brewer's yeast induced pyrexia	<0.001	Hukkeri et al, 2006[28]

10	Peperomia pellucida	Piperaceae	Leaves	Albino rabbits	Ethanolic extract	Boiled milk induced pyrexia	<0.05	Alam khan et al, 2007[29]
11	Radix paeoniae	Paeonaceae	Roots	Wistar rats	Acetone extract	Brewer's yeast induced pyrexia	<0.05	Sapna motwani et al, 2007[34]
12	Taxus wallichiana	Taxaceae	Leaves	Wistar rats	Methanolic extract	Brewer's yeast induced pyrexia	<0.05	Muhammed nisar et al, 2008[44]
13	Mollugo pentaphylla	Molluginaceae	Whole plant	Wistar rats	Methanolic extract	Brewer's yeast induced pyrexia	<0.01	Valarmathi et al, 2010[26]
14	Momordica charantia	Cucurbitaceae	Fruit	Wistar rats	Ethanolic extract	Brewer's yeast induced pyrexia	<0.01	Roshan patel et al, 2010[27]
15	Argyreia speciosa	Convolvulaceae	Roots	Rats	Hydro-alcoholic extract by percolation	Brewer's yeast induced pyrexia	<0.05	Sandeep ahlawat et al, 2010[17]
16	Cuscuta reflexa	Cuscutaceae	Whole plant	Wistar rats	Aqueous and ethanolic extract	Brewer's yeast induced pyrexia	<0.05	Sanjib bhattacharya et al, 2010[23]
17	Capparis zeylanica	Capparaceae	Whole plant	Wistar rats	Methanolic extract	Brewer's yeast induced pyrexia	<0.01	Ranjan pradhan et al, 2010
18	Quisqualis indica	Combretaceae	Leaves	Wistar rats	Methanolic extract	Brewer's yeast induced pyrexia	<0.01	Nitu singh et al, 2010[35]
19	Azima tetracantha	Salvadoraceae	Leaves	Swiss mice	Ethanolic extract	Brewer's yeast induced pyrexia	<0.01	Nargis begum et al, 2011[21]
20	Platycladus orientalis	Cupressaceae	Leaves	Albino rabbits	Petroleum ether	Boiled milk induced pyrexia	<0.05	Amit jaiswal et al, 2011[31]
21	Ficus bengalensis	Moraceae	Leaves	Swiss rats	Ethanolic and aqueous	Brewer's yeast induced pyrexia	<0.05	Sachdev yadav et al, 2011[24]
22	Geniosporum prostratum	Lamiaceae	Bark	Male albino rats	Ethanolic extract	Brewer's yeast induced pyrexia	<0.01	Anil kumar et al, 2011[25]
23	Amaranthus viridis	Amaranthaceae	Whole plant	Male swiss mice	Methanolic extracts	Brewer's yeast induced pyrexia	<0.05	Ashok kumar et al, 2011[19]

24	Plumeria rubra	Apocyanaceae	Leaves	Albino rabbits	Ethanolic	Boiled milk induced pyrexia	<0.05	Vimlesh mishra et al, 2012[32]
25	Pongamia pinnata	Fabaceae	Leaves	Male wistar rats	Methanolic	Brewer's yeast induced pyrexia	<0.01	Anupriya pandey et al, 2012[33]
26	Vitex negundo	Verbanaceaee	Leaves	Male swiss rats	Alcoholic	PGE1 induced pyrexia	<0.05	Jayashree tirumalsetty e al, 2012[36]
27	Ziziphus jujube	Rhamnaceae	Leaves	Wistar rats	Methanolic	Brewer's yeast induced pyrexia	<0.001	Balakrishnan et al, 2012[37]
28	Psidium guajava	Myrtaceae	Dried leaves	Male wistar rats	Ethanolic extract	Yeast induced hyperpyrexia	<0.05	B. V. Owoyele et al, 2012[38]
29	Radix puerariae	Leguminoseae	Roots	Sprague dawley rats	Isoflavanoid puerarin	LPS induced fever	<0.05	Xiu JuanYao et al, 2012
30	Saraca acosa	Caesalpiniaceae	Seeds	Wistar rats	Acetone extract	Brewer's yeast induced pyrexia	<0.01	Sasmal et al, 2012[42]
31	Tecomaria capensis	Bignoniaceae	Leaves	Albino rats	Methanolic extract	Brewer's yeast induced pyrexia	<0.05	Neeraj kumar saini et al, 2012[43]

REFERENCES:

1. Mick NW. Pediatric fever. In: Marx JA, ed. Rosen's Emergency Medicine: Concepts and Clinical Practice. 7th ed. Philadelphia, Pa: Mosby Elsevier; 2009: chap 165.
2. Legget J. Approach to fever or suspected infection in the normal host. Goldman L, Ausiello D, eds. Cecil Medicine, 23rd ed. Philadelphia, Pa: Saunders Elsevier; 2007: chap 302.
3. Robbins & Cotran Pathologic Basis of Disease, 8th Edition
4. Rhoades, R. and Pflanzer, R. Human physiology, third edition, chapter 27 Regulation of body temperature, p. 820 Clinical focus: pathogenesis of fever.
5. McGrath J.A., Eady R.A.; Pope F.M.; Rook's Textbook of Dermatology (7th edition) Blackwell publishing (2004), Pp 3.1-3.6.
6. Shalini Dalal, MD, and Donna S. Zhukovsky, Pathophysiology and Management of Fever, J Support Oncol 2006;4:009–016.
7. Kathryn M. Edwards, The Pathogenesis of Fever.
8. Daniel L. Simmons, David Wagner, and Kenneth Westover, Nonsteroidal Anti-Inflammatory Drugs, Acetaminophen, Cyclooxygenase-2 and Fever, Clinical Infectious Diseases 2000;31(Suppl 5): S211–8.
9. Karen I. Plaisance, Toxicities of Drugs Used in the Management of Fever, Clinical Infectious Diseases 2000; 31(Suppl 5): S219–23.
10. Peter Axelrod, External Cooling in the Management of Fever, Clinical Infectious Diseases 2000;31(Suppl 5): S224–9
11. Kulkarni SK, Handbook of Experimental Pharmacology, 2nd edition, 78-81, 1993.
12. Vogel G, Drug Discovery & Evaluation: Pharmacological Assay, 3 rd edition.
13. McCracker, Thomas New Atlas of Anatomy (2000).
14. Turner RA, Screening methods in pharmacology, Academic Press, London, 61, 1965.
15. Kasting NW. A rationale for centuries of therapeutic bloodletting: antipyretic therapy for febrile diseases. Perspect Biol Med 1990; 33:509–16.
16. Cheng C, Matsukwa T, Sessler DI, et al. Increasing mean skin temperature linearly reduces the core-temperature thresholds for vasoconstriction and shivering in humans. Anesthesiology 1995; 82:1160–8.
17. Sandeep Ahlawat, P.K. Mishra, K. Dalal, Arjun Patra., Antipyretic activity of roots of Argyreia speciosa (burm. f.) Bojer ; Int.J. PharmTech Res., 2010 , 2(4) , 2165-2167.
18. Debprasad Chattopadhyay, Ganeshan Arunachalam, Lopamudra Ghosh, Rajendran K., Asit B. Mandal, S. K. Bhattacharya., Antipyretic Activity of Alstonia macrophylla Wall ex A. DC: An Ethnomedicine of Andaman Islands., J. Pharm. Pharm. Sci., 2005, Vol: 8(3), 558-564
19. Bagepalli Srinivas Ashok Kumar, Kuruba Lakshman, Jayaveera.K.N, Devangam Sheshadri Shekar,

Avalakondarayappa Arun Kumar, Bachappa Manoj., Antioxidant and antipyretic properties of methanolic extract of Amaranthus spinosus leaves; Asian Pacific Journal of Tropical Medicine, 2010 ,702-706.
20. S. Balu, C. Alagesa Boopathi, V. Elango., Antipyretic activities of some species of Andrographis Wall, Ancient Science of Life, 1993, Vol: XVI (3, 4) , 399-402.
21. Tajuddin Nargis Begum, Mohamed Hussain, Muhammad Ilyas, Arumugam Vijaya Anand., Antipyretic activity of azima tetracantha in experimental animals; Int. J. Cur. Biomed. Phar. Res., 2011; Vol: 1(2) , 41 – 44.
22. Amiya Ranjan Padhan, Anuj kumar Agrahari , Ashutosh Meher., A Study On Antipyretic Activity Of Capparis zeylanica Linn. Plant Methanolic Extract; Int. J. of Pharm. Sci. Res., 2010, Vol:1(3), 169-171.
23. Sanjib Bhattacharya, Bodhisattva Roy., Preliminary Investigation on Antipyretic Activity of Cuscuta reflexa in Rats., J. Adv.Pharm. Tech. Res; 2010, Vol:1(1), 83-87.
24. Sachdev Yadav, Mayank Kulshreshtha, Mradul Goswami, Chandana V. Rao and Veena Sharma., Elucidation of Analgesic and Antipyretic activities of Ficus bengalensis linn. Leaves in rats; Journal of Applied Pharmaceutical Science, 2011, Vol: 1(1); 38-41.
25. Anil Kumar Singhal, Vishnu Kumar Singhal, Varun Singh Bhati, Hemendra Gupta., Evaluation of Antipyretic activity of ethanolic extract of Geniosporum prostratum (L.) Benth. Bark., Chronicles of Young Scientists, 2011, Vol: 2(3)., 168-170.
26. R.Valarmathi, A.Rajendran, S.Akilandeswari, R.Senthamarai., Study on Antipyretic Activity of Mollugo pentaphylla Linn in Albino Mice ; Int.J. PharmTech Res., 2010, Vol: 2(4).
27. Roshan Patel, Naveen Mahobia, Nitin Upwar, Naheed Waseem, Hetal Talaviya, Zalak Patel., Analgesic and Antipyretic activities of Momordica charantia Linn. Fruits., J. Adv. Pharm. Tech. Res., 2010, Vol: 1(4), 415-418.
28. V. I. Hukkeri; C. V. Nagathan; R. V. Karadi R.V; B. S. Patil., Antipyretic and wound healing activities of Moringa oleifera Lam. In Rats., Ind. J. Pharm. Sci., 2006, Vol: 68(1): 124-126.
29. Alam khan, Moizur Rahman, Shariful Islam., Antipyretic Activity of Peperomia pellucida Leaves in Rabbit; Turk J Biol; 2008, Vol: 32, 37-41.
30. S. S. Jalalpure ; P. V. Habbu ; M. B. Patil ; R. V. Kulkarni ; C. C. Simpi ; C. C. Patil ; Analgesic and Antipyretic activity of Pergularia extensa in Rats, Indian J. Pharm. Sci., 2002, 493-495.
31. Amit Jaiswal, Niranjan Sutar, Ranju Garai, Manoj Kumar Pati, Abhinav Kumar., Antipyretic activity of Platycladus orientalis leaves extract., IJABPT, 2011, Vol: 2(1).
32. Vimlesh Misra, Sheikh Mubeen Uddin, Vivek Srivastava, Umashankar Sharma., Antipyretic activity of plumeria rubra Leaves extract., Int J Pharm; 2012; Vol: 2(2), 330-332.
33. Anupriya Pandey, Sonu Sharma, Priyanka Chaturvedi., Antipyretic Activity of Pongamia pinnata in Rats; IJPI'S Journal of Pharmacognosy and Herbal Formulations, 2012, Vol: 2(10).
34. Sapna Motwani, Neelesh Malviya, R. K. Goel, K. R. Dutt; Antipyretic activity of Radix paeoniae., Ancient Science of Life, 2007, Vol: XXVII(I), 14-18.
35. Nitu Singh, Pankaj Khatri, Dr. K. C. Samantha, Reena Damor., Antipyretic activity of methanolic extract of leaves of Quisqualis indica Linn., IJPRD, 2010, Vol: 2(9).
36. Jayasree Tirumalasetty, Sheikh Ubedulla, Chandrasekhar. N, P.V. Kishan, Kavitha Rasamal., Evaluation of Antipyretic Activity of Alcoholic Extract of Vitex nigundo Leaves In PGE1 induced pyrexia model in Albino Rats., J. Chem. Pharm. Res., 2012, Vol: 4(6), 3015-3019.
37. Anbarasi Balakrishnan, Parimala Devi Balasubramaniyam, Senthil Kumar Natesan., Antipyretic Activity of Ziziphus jujube Lam. Leaves., J Adv Sci Res, 2012, Vol: 3(3), 40-42.
38. B. Owoyele Victor, O. Jegede, Timothy, O. Soladoye Ayodele., Analgesics and Antipyretic Activities of Ethanolic Extract of Psidium guajava in Rats; Recent Progress in Medicinal Plants; 2005, Vol: 13-Search for Natural Drugs.
39. Jiaix Feng, J. M. Lipton., Eugenol:Antipyretic activity in Rabbits., Neuropharmacology, 1987, Vol: 26(12) , 1778.
40. N. Narayanana, P. Thirugnanasambanthama, S. Viswanathana,U, M. Kannappa Reddya, V. Vijayasekarana, E. Sukumarb., Antipyretic, antinociceptive and anti-inflammatory activity of Premna herbacea roots; Fitoterapia, 2000, Vol: 71, 147-153.
41. N. Narayanan, P. Thirugnanasambantham, S. Viswanathan, V. Vijayasekaran, E. Sukumar., Antinociceptive, anti-inflammatory and antipyretic effects of ethanol extract of Clerodendron serratum roots in experimental animals; Journal of Ethnopharmacology, 1999, Vol: 65, 237–241.
42. Sasmal. S., Majumdar.S, Gupta .M, Mukherjee.A, Mukherjee. P. K., Pharmacognostical, phytochemical and pharmacological evaluation for the antipyretic effect of the seeds of Saraca asoca Roxb., Asian Pacific Journal of Tropical Biomedicine, 2012, 782-786.
43. Neeraj Kumar Saini, Manmohan Singh., Anti-inflammatory, analgesic and antipyretic activity of methanolic Tecomaria capensis leaves extract; Asian Pacific Journal of Tropical Biomedicine, 2012, 870-874.
44. Muhammad Nisar, Inamullah Khan, Shabana Usman Simjee , Anwarul Hasan Gilani, Obaidullah , Humera Perveen; Anticonvulsant, analgesic and antipyretic activities of Taxus wallichiana Zucc., Journal of Ethnopharmacology, 2008, Vol: 116, 490–494.
45. Poir T. Taesotikul, A. Panthong, D. Kanjanapothi, R. Verpoorte, J.J.C. Scheffer ., Anti-inflammatory, antipyretic and antinociceptive activities of Tabernaemontana pandacaqui; Journal of Ethnopharmacology; 2003, Vol: 84, 31-35

46. D. Chattopadhyay, G. Arunachalam, A. B. Mandal, S. C. Mandal., Evaluation of antipyretic activity of leaf extracts of Mallotus peltatus (Geist) Muell. Arg. var acuminatus: A folk medicine Phytomedicine, 2002, Vol: 9, 727–730.