SIR Publishers
CENTER FOR INTERNATIONAL SCIENTIFIC PUBLICATIONS
JOURNAL OF MEDICINE AND PHARMACY
ISSN(Online): 2984-7117
SJIF Impact Factor |(2024): 6.879|
Volume-8, Issue-3, Published |20-03-2025|

MODULATION OF HYPERTHERMIC EFFECT OF PYROGENS BY CALCIUM CHANNEL BLOCKATAROMES

https://doi.org/10.5281/zenodo.15054251

Z.Z. Khakimov[1], A.Kh. Rakhmanov[2], N.B. Bekova[3]

[1]Doctor of Medical Sciences, Professor of the Pharmacology Department of the Tashkent Medical Academy,

[2]Doctor of Medical Sciences, Researcher of the Center for Biomedical Technologies of the Tashkent Medical Academy,

[3]PhD, Senior Lecturer of the Department of Normal and Pathological Physiology of the Urgench Branch of the Tashkent Medical Academy

Abstract.

The effect of calcium channel blockers on the course of fever was studied in animals with various models of pyrexia. It was found that calcium channel blockers significantly modify the hyperthermic effect of pyrogens, which is manifested in a decrease in body temperature. Diltiazem and cinnarizine slightly more than amlodipine, on the model of fever induced by pyrogenal - lipopolysaccharide produced by microorganisms Pseudomonas aeruginosa exhibits a distinct hypothermic effect, not inferior in activity to diclofenac sodium. On the model of hyperthermia caused by baker's yeast, calcium channel blockers exhibit a more pronounced hypothermic effect. The mechanism of antipyretic action of representatives of calcium channel blockers is probably associated not only with the development of vasodilation, but also with a change in the level of proinflammatory cytokines.

Key words

fever, calcium channel blockers, cytokines, hypothermic effect.

Conflict of interest. The authors declare no obvious or potential interests related to the publication of this article.

Introduction.

Perexia (fever) is an increase in body temperature, often caused by physiological processes caused by infectious or non-infectious causes, such as inflammation, allergy, and neoplasms. An important place in the mechanism of fever development is occupied by the release of immunological mediators that disrupt the function of the thermoregulatory center located in the hypothalamus. Normal human body temperature is approximately 37 degrees Celsius (C) or 98.6 degrees Fahrenheit (F) and fluctuates by approximately 0.5 C during the day.

JOURNAL OF MEDICINE AND PHARMACY
ISSN(Online): 2984-7117
SJIF Impact Factor |(2024): 6.879|
Volume-8, Issue-3, Published |20-03-2025|

Changes in body temperature are the result of normal physiological processes throughout the human body, including metabolic changes, sleep/wake cycles, hormonal variability, and changes in activity levels. However, in the case of fever, an increase in body temperature often exceeds 0.5 C and is attributed to a substance that causes fever (pyrogen) [2]. It has been established that fever is often mediated by the pyrogenic activity of prostaglandins [PGF2], which is formed from arachidonic acid with the participation of cyclooxygenase [COX]. Based on this, COX inhibitors - non-steroidal anti-inflammatory drugs (NSAIDs) are used to treat fever [1, 2]. However, the latter quite often causes the development of side effects up to death [3-10]. Therefore, the search for anti-inflammatory drugs that differ in the mechanism of action of NSAIDs is an urgent problem of modern pharmacology. Along with this, it is necessary to take into account that the main diseases of a non-inflammatory nature are often accompanied by inflammatory diseases [11]. For example, calcium channel blockers (CCBs) used as hypotensive, antianginal, antiarrhythmic agents [12, 13] can have a certain effect on the hypothermic effects of pyrogens. This assumption is based on the fact that this group of pharmacological agents exhibit distinct anti-inflammatory, analgesic and antiproliferative effects [14-17]. At the same time, the specifics of the body's response to the effects of pyrogens against the background of the use of CCBs require a separate in-depth study. The purpose of this work was to study the effect of CCB representatives on the course of fever induced by various pyrogens.

Materials and methods of research.

To evaluate the antipyrogenic activity of BKK, sexually mature male rats weighing 185-200 g were used. They were obtained from the nursery of the Department of Sanitary and Epidemiological Surveillance of the Main Medical Department under the Administration of the President of the Republic of Uzbekistan. All experimental animals were kept in standard vivarium conditions with free access to food and water, natural alternation of light and darkness. Before the experiment, the laboratory animals were carefully examined, weighed, their age, sex, and motor activity were taken into account. Throughout the preparation for the experiment and during its implementation, the laboratory animals were kept in a vivarium at a temperature of 22-24 ° C, humidity of at least 50%, in a well-ventilated room and day / night light mode, in standard plastic cages, with a standard diet. The daily requirement is made up in accordance with the age of the animals. All laboratory animals participating in the experiment were healthy and active before the experiment. The following drugs were used in the experiments: diclofenac sodium (Hemofarm LLC, Russia); diltiazem (Alkaloid AD Skopje, Republic of North Macedonia), amlodipine (Ozon Pharm LLC, Russia), cinnarizine (Sopharma JSC, Bulgaria). The study was conducted in accordance with regulatory

SIR Publishers
CENTER FOR INTERNATIONAL SCIENTIFIC PUBLICATIONS
JOURNAL OF MEDICINE AND PHARMACY
ISSN(Online): 2984-7117
SJIF Impact Factor |(2024): 6.879|
Volume-8, Issue-3, Published |20-03-2025|

documents in the field of handling drugs, the principles of good laboratory practice (GLP), as well as with the "Rules for conducting laboratory work using experimental animals", the rules given in the European Convention for the Protection of Vertebrate Animals used for Experimental Research and other Scientific Purposes (ETS No. 123) Strasbourg 18.03.1986.

The antipyretic activity of the above drugs in all groups of animals was assessed by the ability to reduce body temperature against the background of hyperthermia caused by the introduction of pyrogenal. The pyrogenic reaction was modeled by intravenous administration of pyrogenal at a dose of 5 μg/kg [18]. Sodium diclofenac at a dose of 10 mg/kg; diltiazem and amlodipine - 20 mg/kg, cinnarizine - 50 mg/kg were administered intragastrically 15 minutes before the injection of pyrogenal. The hypothermic activity of the drugs was assessed by the magnitude of the decrease in body temperature compared to the control group that did not receive the drug. The hypothermic effect of the drugs was calculated by the ratio between the increase in temperature from the initial level in the control and experimental groups. The control groups of animals were administered an equivalent volume of distilled water intragastrically. To measure rectal temperature (T), an electric thermometer TPEM - 1 (NPO Medfizpribor, Kazan, Russia) was used before and after the introduction of pyrogen in dynamics for 3 hours with an hourly interval. Temperature readings were recorded with an accuracy of 0.1°C.

In the next series of experiments, the most widely used model of fever caused by Perak yeast was used to assess the hypothermic activity of BCC.

Before the introduction of the yeast suspension, the basal level of rectal temperature (Tnach) was measured in animals, immediately after which a 20% suspension of baker's yeast (10 ml/kg), preheated in a water bath to 37°C, was subcutaneously injected into the area between the shoulder blades [19]. It is worth noting that heating the yeast suspension is important, since without heating, hyperthermia is observed no earlier than after 16-18 hours. After 6 hours and then every hour after the yeast injection, rectal temperature was measured to determine the dynamics of fever. The peak of fever (Tmax) was noted after 8 hours, animals whose temperature increased by more than 0.5°C were included in the further experiment. At the height of the fever (i.e. 8 hours after the introduction of the baker's yeast suspension), the rats were administered diclofenac sodium intragastrically using a special metal probe at a dose of 10 mg / kg; diltiazem and amlodipine - 20 mg / kg, cinnarizine - 50 mg / kg. Then, to assess the antipyrogenic activity of the above groups of CCB drugs, the temperature was measured after 1 hour (T1h), 2 hours (T2h), 3 hours (T3h). Since fevers activate numerous neural pathways and factors, such as interleukin - 1 (IL-1) and tumor necrosis factor alpha (TNFα), we also studied the effect of CCB on the level of

JOURNAL OF MEDICINE AND PHARMACY
ISSN(Online): 2984-7117
SJIF Impact Factor |(2024): 6.879|
Volume-8, Issue-3, Published |20-03-2025|

cytokines in the blood in a model of carrageenan inflammation in mature laboratory animals [20]. Groups of 6 individuals were formed each. Diclofenac sodium at a dose of 10 mg / kg; diltiazem and amlodipine - 20 mg/kg, cinnarizine - 50 mg/kg were administered intragastrically one hour before the injection of flagogen. After the introduction of 1% carrageenan solution (Sigma-Aldrich, USA) into the hind paw, after 3 hours under light ether anesthesia, the animals were decapitated and blood was collected, in which the concentration of interleukins IL-1β and TNF-α in the blood serum was determined by the method of solid-phase enzyme immunoassay (commercial ELISA kits manufactured by Human Diagnostics and Vector-Best, Russia).

The results of the obtained data were processed statistically using the standard Statistika for Windows program package using the well-known method of variation statistics. The data are presented as M ± m, where M is the mean value, m is the standard error of the mean value. Differences between groups were identified using Student's t-test and were considered statistically significant at $p < 0.05$.

Research results and their discussions

Fever is a condition in which there is an increase in body temperature above 37.5°C. Exogenous pyrogens such as bacteria or viruses in the body are phagocytized by lymphocytes and activated. Activated lymphocytes secrete cytokines such as interleukin-1, which stimulate the thermoregulatory center, and the stimulated thermoregulatory center increases the "set point" of body temperature [21].

The results of the experimental studies showed that intravenous injection of bacterial lipopolysaccharide - pyrogenal clearly increases the body temperature of experimental animals. Thus, after 1, 2 and 3 hours from the beginning of the experiment, the rectal temperature increased by 1.9%, 3.7% and 3.2% from the initial value and reached 40.0°C versus 38.6°C from the initial value. In contrast, the pyrogenic effect of pyrogenal in animals receiving BCC was somewhat different, that is, the degree of hyperthermia development was clearly low compared to the control. The introduction of pyrogen into animals pre-treated with Amlodipine resulted in an increase in rectal temperature by 1.5% after 1 hour, by 2.8% after 2 hours and by 2.5% after 3 hours. As can be seen from the presented material, the pyrogenic activity of pyrogenal was clearly low compared to the control. We noted a somewhat pronounced effect of BCC in animals preventively treated with dilteazem, in which the rectal temperature increased after 1, 2 and 3 hours by 1.4%, 2.1% and 1.8%, respectively. We found almost the same effect in animals pre-treated with cinnarizine. From the data in Table 1 it is evident that the hypothermic activity of the reference NSAID drug, sodium diclofenac, in the studied observation periods was 1.3-1.4%. Thus, the pyrogenic effect of pyrogenal - lipopolysaccharide

SIR Publishers
CENTER FOR INTERNATIONAL SCIENTIFIC PUBLICATIONS
JOURNAL OF MEDICINE AND PHARMACY
ISSN(Online): 2984-7117
SJIF Impact Factor |(2024): 6.879|
Volume-8, Issue-3, Published |20-03-2025|

produced by microorganisms Pseudomonas aeruginosa against the background of the action of BCC is clearly reduced, which indicates the presence of antipyretic action of this group of drugs. It is noteworthy that the indicated drugs - BCC in their hypothermic activity are noticeably not inferior (especially dilteazem) to the hypothermic effect of sodium diclofenac. Analysis of the obtained results allows us to assume that the antipyretic effect of BCC is associated with its interaction with microbial lipopolysaccharide or there is another mechanism for the identified effect.

Table 1

Antipyretic activity of amlodipine, diltiazem, cinnarizine and diclofenac sodium in pyrogenital fever in rabbits (M±m, n=6).

Groups	dose, mg/kg	**Tnach Δt ± m, °C**	**T1h Δt ± m, °C**	**T2h Δt ± m, °C**	**T3h Δt ± m, °C**
Control	-	38,63±0,19	39,37±0,14* 0,74±0,06	40,07±0,11* 1,44±0,11	39,87±0,13* 1,24±0,09
Amlodipine	20	38,47±0,16	39,07±0,18* 0,60±0,05	39,57±0,13* 1,10±0,09	39,43±0,11* 0,96±0,07
Dilteazem	20	38,36±0,14	39,00±0,15* 0,64±0,06	39,27±0,16* 0,91±0,07	39,17±0,13* 0,81±0,07
Cinnarizine	20	38,43±0,11	39,03±0,13* 0,60±0,06	39,30±0,12* 0,87±0,07	39,20±0,10* 0,77±0,05
Diclofenac	10	38,57±0,13	39,07±0,16* 0,50±0,05	39,23±0,18* 0,66±0,06	39,10±0,19 0,53±0,04

Note. *Here and below, "*" indicates reliable differences (Student p≤0.05) compared to the initial temperature. The numerator shows the absolute body temperature, and the denominator shows the difference in elevated temperature by the hour.*

To clarify this assumption, the following series of experiments were conducted, in which the features of the development of fever induced by baker's yeast against the background of the action of BCC were studied.

The results of this series of experiments showed that subcutaneous administration of a suspension of baker's yeast leads to an increase in rectal temperature at most 8 hours after the start of its administration. Thus, compared with the initial temperature in control animals, the rectal temperature increased by 3.9%. The noted effect gradually weakened in the subsequent hours of observation, but even by the end of the third hour of observation it remained high by 2.0%.

Consequently, as noted by other researchers, brewer's and baker's yeast in experimental animals significantly increases body temperature indicating the development of fever [19, 22, 23].

SIR Publishers
CENTER FOR INTERNATIONAL SCIENTIFIC PUBLICATIONS
JOURNAL OF MEDICINE AND PHARMACY
ISSN(Online): 2984-7117
SJIF Impact Factor |(2024): 6.879|
Volume-8, Issue-3, Published |20-03-2025|

Unlike bacterial lipopolysaccharides, the pyrogenic effect of baker's yeast is clearly high, but develops after a certain latent period with its subcutaneous administration (8-16 hours). In animals receiving preventive CCB, subcutaneous administration of baker's yeast also led to the development of a feverish state. CCB preparations were administered orally during the maximum increase in rectal temperature. As can be seen from the data in Table 2, in animals receiving Amlodipine, the level of rectal temperature was low compared to the control.

Table 2

Changes in body temperature of rats in the model of yeast-induced fever after the administration of amlodipine, diltiazem, cinnarizine and diclofenac (M ± m, n = 6)

Groups	dose, mg/kg Tnach	Δt ± m, °C Tmax	Δt ± m, °C T1h	Δt ± m, °C T2h	Δt ± m, °C T3h	Δt ± m, °C
Control	-	38,51±0,04	40,02±0,12* 1,51±0,12	39,72±0,08* 1,21±0,09	39,58±0,10* 1,07±0,08	39,27±0,09* 0,76±0,06
Amlodipine	20	38,45±0,08	39,93±0,15* 1,48±0,13	39,37±0,12* 0,92±0,04	39,11±0,14* 0,66±0,06	38,92±0,15* 0,47±0,07
Dilteazem	20	38,21±0,09	39,66±0,10* 1,45±0,11	39,22±0,16* 1,01±0,07	39,02±0,15* 0,81±0,05	38,85±0,14 0,64±0,05
Cinnarizine	20	38,38±0,05	39,90±0,17* 1,52±0,13	39,22±0,18* 0,84±0,06	38,95±0,16* 0,57±0,06	38,81±0,16 0,43±0,03
Diclofenac	10	38,31±0,07	39,75±0,17* 1,44±0,13	39,10±0,18* 0,79±0,07	38,84±0,14* 0,53±0,05	38,71±0,17 0,40±0,03

Thus, in these groups of animals after 1.2 and 3 hours the rectal temperature decreased by 37.8%, 55.4% and 68.2% from the beginning of Amlodipine administration. It is noteworthy that the degree of temperature decrease was clearly low against the background of Amlodipine compared to the control. We found almost the same effect in direction and degree of action in rats receiving Dilteazem. In contrast, in animals receiving Cinnarizine, the development of fever was clearly low, but the degree of decrease in rectal temperature over time was somewhat high, especially compared to the group of animals receiving Dilteazem. It should be noted that in rats receiving sodium diclofenac, the degree and direction of hypothermia development were identical to those in the group receiving Cinnarizine. From the data presented, it is clear that BCC drugs prevent the development of fever induced by baker's yeast. In their action, they have the same direction of effect as described in the previous series of experiments using pyrogenal.

JOURNAL OF MEDICINE AND PHARMACY
ISSN(Online): 2984-7117
SJIF Impact Factor |(2024): 6.879|
Volume-8, Issue-3, Published |20-03-2025|

It can be assumed that calcium channel blockers (e.g. nifedipine, verapamil, diltiazem) reduce the influx of calcium ions through L-type voltage-dependent calcium channels into vascular smooth muscle cells, cardiomyocytes and neurons. Their hypothermic effect is associated with several key mechanisms. A decrease in vascular tone, when calcium channels are blocked, leads to relaxation of vascular smooth muscles, causing vasodilation. Dilation of peripheral vessels promotes increased heat transfer, which can lead to a decrease in body temperature. A decrease in metabolic activity, since calcium plays an important role in the regulation of cellular metabolism and thermogenesis. A decrease in calcium intake reduces mitochondrial activity and processes associated with heat production. Some calcium channel blockers can penetrate the blood-brain barrier and affect the hypothalamic thermoregulatory center. This can lead to a decrease in the set point of body temperature. Decreased intracellular calcium concentrations in cardiomyocytes result in decreased cardiac contractility, decreased cardiac output, and decreased blood flow velocity. This, in turn, reduces heat production in the body.

In summary, the hypothermic effect of calcium channel blockers is likely mediated by a combination of vasodilation, decreased cellular metabolism, effects on the thermoregulatory centers of the central nervous system, and inhibition of myocardial contractility.

The development of fever involves numerous neural pathways and factors, such as interleukin-1 (IL-1) and tumor necrosis factor alpha (TNFα). Accumulating evidence from animal models suggests that TNFα and IL-1 levels are elevated in baker's yeast fever [22, 23]. This suggests that levels of these factors may be used as indicators of disruption of the hyperthermic effect of pyrogens. The results of the conducted studies showed that in animals with aseptic inflammation the level of IL-1β increased by 2.5-4.0 times, and TNFα by 2.0-3.0 times. At the same time, in the groups of animals receiving CCB they statistically significantly decreased: under the influence of amlodipine by 44.7% and 39.9%, and diltiazem by 62.6% and 49.8%, respectively. Almost the same changes were found in animals receiving cinnarizine. It is evident that CCB has a distinct effect on the content of the studied cytokines, manifested in a decrease in their level. These data allow us to assume that proinflammatory cytokines are indicators reflecting the development of hyperthermia, as well as the antipyretic effect of CCB. The above experimental material allows us to conclude that in terms of increasing the effectiveness of pharmacotherapy with calcium channel blockers, it is necessary to take into account their modeling effect on the action of pyrogens of various origins, especially in patients with comorbid inflammatory pathology.

Conclusions

1. Calcium channel blockers significantly modify the hyperthermic effect of pyrogens, which manifests itself in a decrease in body temperature.

2. Diltiazem and cinnarizine, somewhat more than amlodipine, exhibit a distinct hypothermic effect on the model of pyrogenal-induced fever - a lipopolysaccharide produced by Pseudomonas aeruginosa microorganisms, not inferior in activity to sodium diclofenac.

3. On the model of hyperthermia caused by baker's yeast, calcium channel blockers exhibit a more pronounced hypothermic effect.

4. The mechanism of antipyretic action of calcium channel blockers is probably associated not only with the development of vasodilation, but also with changes in the level of proinflammatory cytokines.

LIST OF REFERENCES

1. Захарова И.Н., Бережная И.В., Сугян Н.Г. и соавтор. Лечение лихорадки при острых респираторных инфекциях верхних дыхательных путей у детей. *Медицинский совет*. 2022;16(1):88–95. https://doi.org/10.21518/2079-701X-2022-16-1-88-95

2.Balli S., Shumway K.R., Sharan S. Physiology, Fever. 2023 Sep 4. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–. PMID: 32966005

3.Карева Е.Н., Олейникова О.М., Сереброва С.Ю. и соавторы. Побочные эффекты нестероидных противовоспалительных средств и пути их профилактики. Экспериментальная и клиническая фармакология. 2022; 85(3):33-44.

4. Муфазалова Н.А., Валеева Л.А., Р.А. Давлетшин Р.А. и соавторы. Нежелательные лекарственные реакции. Взаимодействие лекарственных средств. Часть I. Нестероидные противовоспалительные препараты// учеб. пособие— Уфа: ФГБОУ ВО БГМУ Минздрава России, 2020. — 195 с.

5.Хакимов З.З., Рахманов А.Х., Мавланов Ш.Р. Противовоспалительная активность смеси лекарственных растений. ООО «TIBBIYOT NASHRIOTI MATBAA UYI», Ташкент. -2022. - 228 с.

6.Чеботарева Н.В., Лысенко Л.В. Поражение почек, ассоциированное с нестероидными противовоспалительными препаратами. Нефрология и диализ. 2022;24(3):431-440.

7.Gunaydin, C., Bilge, S. Effects of Nonsteroidal Anti-Inflammatory Drugs at the Molecular Level. The Eurasian Journal of Medicine. 2018;50(2):116-121.

8.Prozzi R.G., Cañás M., Urtasun M.A et al. Riesgo cardiovascular de los anti-inflammatories no esteroideos. MEDICINA (Buenos Aires). 2018;(78):349-355.

9.Sikorska D., Chlabicz S., Rydzewska G et all. Nonsteroidal anti-inflammatory drugs in clinical practice — are there any new reports? Rheumatology Forum REVIEW ARTICLE. 2024;10(1):26–37.

10.Ying X. H., Bao D. N., Jiang H. Y., Shi Y. D. Maternal non-steroidal anti-inflammatory drug exposure during pregnancy and risk of miscarriage: a systematic review and meta-analysis Eur. J. Clin.Pharmacol. 2022;78(2):171 – 180.

11. Хакимов З.З., Рахманов А.Х., Бекова Н.Б. Блокаторы кальциевых каналов – модуляторы асептического воспаления. Монография. Издательство ООО «TIB NASHR», Ташкент.2025. - 134 с.

12.Мокров Г. В. Кардиопротекторные средства с биароматической структурой. Часть 1. Блокаторы кальциевых каналов. Фармакокинетика и фармакодинамика. 2021;(4):3–17. https://doi.org/10.37489/2587-7836-2021-4-3-17.

13.McKeever R.G., Patel P., Hamilton R.J. Calcium Channel Blockers. [Updated 2024 Feb 22]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482473/

14. Khakimov Z. Z., Rakhmanov A. Kh. Bekova N. B., Shukurlaev K. Sh Influence of the potential dependent calcium channel blockers to the development of carrageenan-induced aseptic inflammation. Natl J Physiol Pharm Pharmacol. 2021; 11(4):436-440.

15.Хакимов З.З., Рахманов А.Х., Шукурлаев К.Ш., Бекова Н.Б. Особенности течения экссудативной и пролиферативной фазы воспаления при применении блокаторов кальциевых каналов. Методические рекомендации. Ташкент. 2021: 24 с

16.Khakimov Z. Z., Bekova N. B, Rakhmanov A. Kh., Zaitseva O. A. The Course of Freund's Adjuvant Induced Chronic Arthritis under the Influence of Calcium Channel Blockers. American Journal of Medicine and Medical Sciences 2022, 12(2): 183-188.

17. Khakimov Z.Z., Rakhmanov A. Kh., Bekova N. B. The effect of calcium channel blockade on pain sensitivity in experimental animal. American journal of applied medical science. 2025; Vol. 3 No. 2: 11-21.

18.Покровский М.В., Бобынцев И.И., Корокин М.В. и соавт. Сравнительное фармакологическое и токсикологическое исследование препаратов "Пентальгин плюс" и "Пентальгин - Н"//Курский научно-практический вестник «Человек и его здоровье». 2007;(4):22-29.

19. Khakimov, Z. Z., and G. Yu Djanaev. "Askarov OO Study Of the Effect of a Mixture of Extracts of Medicinal Plants on the State of the Gastric Mucosa in

Gastropathy Induced by Indomethacin." *Eurasian Medical Research Periodical* 19 (2023): 90-95.

20. Khakimov Z. Z., RakhmanovA.Kh. Yuldashev J. I. Study of the Influence of Cotton Cellulose Derivatives on the Course of Carrageenan-Induced Arthritis in Rats. American Journal of Medicine and Medical Sciences 2021; 11(12): 926-929. DOI: 10.5923/j.ajmms.20211112.17

21. Osilla EV, Marsidi JL, Shumway KR, et al. Physiology, Temperature Regulation. [Updated 2023 Jul 30]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK507838/

22. Zhang X., Wang Y., Li1 Sh. et all. The Potential Antipyretic Mechanism of Gardeniae Fructus and Its Heat-Processed Products with Plasma Metabolomics Using Rats with Yeast-Induced Fever. Frontiers in Pharmacology. May 2019 Volume 10 | Article 491.1-12. | www.frontiersin.org.

23. Dangarembizi R., Erlwanger K. H., Rummel C. et all. Brewer's yeast is a potent inducer of fever, sickness behavior and inflammation within the brain. Brain Behav. Immun.2018; 68, 211–223. doi: 10.1016/j.bbi.2017.10.019