Original Article

TIPS Trends in Pharmaceutical Sciences 2018: 4(1): 59-82.

A Systems Biology Approach to Hot and Cold Theory

Maryam Roodaki[1], Zohreh Abolhassanzadeh[2,*], Iman Karimzadeh[4], Pouya Faridi[2,3,*]

[1]Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran.

[2]Pharmaceutical Sciences Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.

[3]Infection and Immunity Program, Biomedicine Discovery Institute and Department of Biochemistry and Molecular Biology, Monash University, Melbourne, Victoria, Australia

[4]Department of Clinical Pharmacy, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran.

Abstract

The use of traditional medicine as an important part of complementary/alternative medicine spread nowadays all around the world. Something that is due to the lack of effectiveness of modern medicine in treating some disease especially chronic disease. Since one of the most important theories beside traditional medicine is the concept of "temperaments" and this is very close to the concept of personalized medicine, which is taken into consideration nowadays. It is important to investigate what really temperament is and also reach a precise meaning and criteria for determining it. For reviewing all the researches that have been done on temperaments till today, the most popular database like PubMed, Scopus, Google scholar, science direct and etc. were searched for keywords Hot and cold, temperaments, hot and cold medicine, hot and cold nature, hot and cold parameters till September 2015. The results show that there are some physiological and metabolic criteria, genes and networks and metabolite that contribute in determining the temperaments not only in body but also in disease, foods and drugs. Despite the presence of all these detailed data the lack of a comprehensive practical criteria for temperament is still obvious, so we try to gather all data to reach that in its best way.

Keywords: Hot and Cold, Personalized medicine, Temperament, Traditional Medicine, Systems Biology.

1. Introduction

1.1. Complementary/ alternative medicine

The terms "complementary/alternative medicine" or CAM refer to some health care practices that are beside the dominant health care system and not integrated into it. They are used interchangeably with traditional medicine in some countries. Over the last twenty years, due to the lack of sufficient result on treating some disease by current modern medicine, specially prevention and management of chronic disease, and also due to the advantages that people see from CAM, like its cost-effectiveness beside its performance, there has been a lot of tendency toward it (1). World Health Organization (WHO) confirmed this claim by estimating that most people in developing nations receive most of their health care from traditional or complementary health systems. Maybe this is due to the lack of modern physician; however, this is not. Because investigations in the United States, the United Kingdom, and Australia show that the 50 %, and in France, 75% of the population report the use of alternative medicines, that is not from the lack of physician but also due to the society's tendency toward CAM (2). For all these reasons during these years many scientists put their effort into investigating the efficacy and safety of CAM

Corresponding Author: Pouya Faridi & Zohreh Abolhassanzadeh, Pharmaceutical Sciences Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.
Email: Pouya.faridi@monash.edu ; abolhasanz@sums.ac.ir

Recieved: 29/01/2018; Accepted: 28/02/2018

and understanding the mechanism of its action and it is standardization (1).

1.2. Temperaments and alternative medicine

One of the most critical parts of CAM is Traditional Medicine (TM) which rooted in the culture of each country. Traditional medicine is based on the theories, beliefs, and experiences indigenous to different cultures used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness. TM has different theories in every country and of all the existing theories "Temperaments," that is the hot and cold pattern in a body, foods, etc. is the most important and popular one that contribute in health maintenance and disease treatment in a very personalized way.

The initial root of humoral medicine and temperaments is not clear. Hippocrates wrote one of the earliest well-established documents. Nowadays by referring to different references we see that this theory exists in TM of different countries all over the world from Iran (Persian medicine or PM) and China (Traditional Chinese medicine or TCM) in Asia to Latin America's country and Africa, and they all affected by the first theory from Hippocrates.

Temperaments in these traditional medicines referred to all body, illnesses, foods and drugs and divided into two main categories of hot and cold. The definition and determining factors of hot and cold differ in every country. Based on different traditional medicine different criteria determine the state of the healthy body from the hot/cold sight of view and offsetting from this state cause illnesses. This is also true about foods and drugs. They have different temperaments, by their component so that they can be harmful or useful by way of their use.

Based on traditional medicine theories by identification the temperaments of the body, food and also disease there can be a better life for healthy people and also a sufficient treatment for disease because every person with specific temperaments is susceptible to a particular disease and need specific treatments.

Despite the importance of temperaments theory the absence of comprehensive scientific explanation based on today medicine is felt, however, some research has been done lately.

The purpose of this study is to collect the result of researchers that have been done on temperaments till today and also light up the route ahead to an inclusive definition for hot and cold temperaments.

2. Methods

2.1. Using Research databases

For investigating data about hot/cold theory keywords including hot and cold, temperaments, hot and cold medicine, hot and cold nature, hot and cold parameters were searched in some databases such as PubMed, Scopus, Google scholar, science direct and *etc*. till September 2015.

2.2. Using Genomic and proteomic databases

After gathering all data from all of the studies, Panther, Uniprot and Funrich database were used for reviewing collected data in more accurate way and achieve a functional overview of the genomic data.

3. Results

Nineteen related articles were found. Based on these articles the hot/cold theory exist in most of the traditional medicine of different countries for example Iran, China, India, Greek, Africa and also Latin America, but there are some differences in basic definitions.

3.1. Persian Medicine (PM) and hot/cold

According to PM, temperaments or *Mizaj* are coming from interaction between different elements. Based on an ancient theory, four elements of fire, water, soil and air have their own quality and characteristics determined by interaction of opposite qualities of small particles exist in these elements and the interaction as well as balance between these four elements result in body, foods and medicine characteristics. A human body is healthy till these elements are in balance, so based on it there are nine groups of temperaments including moderate state, four simple *Mizaj* (hot, cold, wet and dry) and four combined *Mizaj* (hot and wet, hot and dry, cold and wet, cold and dry). These patterns not only refer to human but

also to every medicine and food. The offset of these temperaments balance leads to different diseases and determine the treatments. Furthermore each member of these groups is more susceptible to some diseases and also need different recommendation for health and prevention (3, 4).

3.2. Traditional Chinese medicine (TCM) and hot/cold

Traditional Chinese medicine has been used till ancient times. The hot or cold property of every constitution, disease, food and drug in TCM follow the rule of yin and yang and determined by the internally and externally balance of these two. Yang produces heat and yin produces coldness. The first and the most important goal of TCM is to reestablish the balance between yin and yang, so based on one of the most important TCM guideline "Hot medications cure cold and cold medications cure hot". There are some differences between hot/cold manifestations in Persian and Chinese medicines. Manifestation is external body symptom, but pattern is a higher level of generalization of an illness which is the conclusion of body signs. Despite the pattern, manifestations do not represent the true nature of illness. Pattern identification in TCM has been done by subjective "the four diagnostic methods" composed of section, listening and smelling, inquiring and palpation (5-8).

3.3. Ayurveda and hot/cold

Ayurveda is a medical system primarily practiced in India and includes diet and herbal remedies, emphasizing on body, mind and spirit in disease, prevention and treatment. There is also hot/cold definition in Ayurveda that only refers to food but not to the body. According to its theory every single person has a specific body type of three categories named Vata, Kapha, and Pitta. Everyone has all of these three in his/her body but one of them paly the major role and determine body type. Based on these body types people should fallow their appropriate diet and lifestyle, for example Pitta type is calmed by cooling foods. But in Ayurveda foods categorized into two groups of hot and cold that is refer to its potency and its effect on mind and body and it has nothing to do with temperature, for example hot foods are beneficial for digestion, but high consumption of them can lead to various overheating ailments like ulcers, rashes, and gastritis. Cold foods are helpful in offsetting the effects of heating foods and for cooling down Pitta.

3.4. Greek Traditional medicine

Based on Greek theory humankind and animals are consisting of four humors named Blood, phlegm, choler or yellow bile and melancholy or black bile. Balance of these humors determines the physical constitution and temperaments of a person. This balance is not same in all of the people and everybody has his own balance as well as temperament. It is important for the physician to determine everybody humoral balance so they can follow every change that causes an illness (9). These temperaments (hot, col, dry and wet) can also assign to food, drinks and diseases.

3.5. Latin America's Traditional medicine

In Latin America there is a lot of theories and hypothesizes about the root of hot/cold theory and the philosophy behind it. Based on the most reliable theory Latin America's TM come from Greek TM and the philosophy of blood, phlegm, black bile, yellow bile and their balance. Then some folk beliefs that related to emotionally hot disorders such as evil eye and anger added to it, so nowadays there is a general theory of hot and cold about both illness and foods. Illness is divided to hot and cold base on their symptoms and severity, for example diarrhea could be hot since it's come with blood or it is cold since white phlegm or mucus comes out. Food is also divided into hot and cold based on different criteria for example there is a general agreement that dark colored foods are hot and light colored foods are cold or plants that have pungent odor (like peppermint) or bitter taste are warm. In Latin America theory the property of food also depends on how they prepared so housewives try to mediate hot/cold during cooking so can maintain the healthiness. Like all other theories around the world in Latin America each type of disease treat with opposite type of medicine (10, 11).

3.6. African traditional medicine

There are several types of African traditional medicine practices in the region that all of them based on curative, apprenticeship (training), promotional and rehabilitation services for all ages (12). One of the theory beside African TM is the theory of KelTamasheq population in Burginafasu of Niger that shows completely another explanation for hot and cold. Based on their believes, KelTamasheq specialist uses Tekusse (heat) and Tessumde (coldness) to classify illness, symptoms, food, body states, places, medicine etc. They believe that in a body hot/cold determined by blood and water. Blood where there should not be is a sign of hot (for example nose bleeding, fleeing blood pressure behind eye, blood in urine/vomiting) and lack of blood where there should be is a sign of cold (for example amenorrhea, absence of blood after child birth). On the other side of spectrum, water where there should not be a sign of cold (for example watery diarrhea, sinusitis with nose runs and watery vaginal discharge). There are three forms of patterns in temperament: hot (Tekusse), cold (Tessunde) and hot plus cold. Each of these patterns has three types: hot/cold illness, congenitally hot/cold, pathological hot/cold and like other theories discussed before a healthy body is hot-cold equilibrium, furthermore in KelTamasheq beliefs different states may coexist in the same person. For example, someone can be cold in his/her lower body but hot in his/her upper body and head. Diseases and symptoms also are divided into hot/cold and There are two symptoms that if accompany with an illness, it is a sign of cold, first is Talawayat (the pain in one side of head with running eye) and acalalam (a swelling that grows and move). Hot temperature and foods cause pathological Tekusse and getting wet or physically cold cause pathological Tessumde. This is very important because the nature of illness determines the treatment. Every disease treats with the opposite pattern foods and treatments. If the treatment is so strong, the nature of illness can change too. Cold diseases are rarer, harder to treat and more insidious, in the opposite of hot diseases also women are more prone to cold illness because of the case of blood in different stage of their life.

Based on KelTamasheq beliefs, foods are also hot and cold, but there is not a uniformly consistent taxonomy for them and they may change by the way of different preparation. For example, a grain is hot and dry when it is boiled and is cold when it is in gruel. Over all adding medicinal leaves, water, milk and sugar can change food pattern. Because of this different pattern, mixing of some food is avoided because they are not compatible for digestive system and the consumers' insides will become dirty. Along with this classification of food, there is another classification to heavy and light that refer to ease of digestion. Most of the hot foods are heavy, while cold foods are light. KelThamasheq specialist believes that every food has a hot/cold pattern, but is not general and systemic. It depends on person circumstances and conditions (13).

3.7. Efforts to investigate what hot and cold means?

Nowadays, these theories in traditional medicine are become more realistic by some researches that have been done during these years and look to this topic from different aspect. Some article try to find a molecular explanation for hot/cold both in the body and in food, others try to approach more physiological or clinical explanation and some works on this definition in drugs and foods.

3.8. Healthy Person

3.8.1. Physiological approach in healthy person

On the basis of traditional medicine systems, each person has its own original temperament which affects all aspects of his life. In addition to general temperament, each organ also has its own temperament which has directed relation with the disease which may happen in that organ.

It is shown that in PM (Persian medicine) each person temperament is associated with age, sex, environment, body temperature and also BMR (basal metabolic rate). Based on this study, people with warm temperament have a higher BMR and higher amount of TEF (thermic effect of food), while the cold one has a lower MBR and TEF (14).

According to TCM the manifestation of hot/cold that is visible body symptoms are different in hot/cold temperaments and all concluded to

Table 1. Body criteria to determine temperament type.

Hot	Cold	Ref
Higher BM	Lower BMR	(14)
Higher TEF	Lower TEF	(14)
Blood where there should not be	Lack of blood where there should be	(13)
Higher heart rate	Lower heart rate	(5)
Aversion to heat, preference for cold	Aversion to cold, preference for heat	(6)
Thirst with a preference for cold Beverages	No thirst or preference for hot beverages	(6)
Reddish complexion	White complexion	(6)
Warm limbs	Cold limbs	(6)
Dry bound stool; reddish-yellow urine	Semi-liquid stool; long voiding of clear urine	(6)
Reddish tongue body with yellow, dry coating	Pale tongue body with white, slippery, moist coating	(6)

body patterns. The cold pattern that manifests from the decline of activity of internal organs cause some clinical manifestations. These symptoms are based on the loss of warmth. The symptoms of an external and internal cold are different. For example, aversion to cold, cold limbs, long voiding of clear urine, etc. The hot pattern that caused by increasing of yang rate and loss of yin, and also hyperactivation of internal organs. Table 1 shows the hot pattern as the same of the cold pattern has some main additional symptoms like a preference for coldness, thirst for a cold beverage, dry bound stool, *etc*. (6).

3.8.2. A Molecular approach in healthy person

Based on another study, the temperament can indicate by mitochondrial proteins by the use of HPLC. For this purpose mitochondrial protein of peripheral mononucleotide cells (PBMC) were extracted and two-dimensional chromatography-mass spectrometry has involved, seeing the differences between peaks and their intensity in hot/cold temperaments. These differences are due to glycoside and phosphate group from Post Translation Modification in the cold/dry group that influence on protein activity/stability, and also because of different phenotype (some protein with various kinetic properties) (15).

3.9. Disease

3.9.1. Clinical approach to hot and cold in patients

There are some efforts for investigating the patterns of disease or the effects of body patterns on promotion or treatment of disease. As seen below most of the studies have been done on rheumatoid arthritis (RA).

Table 2. The pathway contribute in hot/cold herbs.

Hot	Ref	Cold	Ref
Cancer	(17)	Cellular assembly and organization	(17)
Endocrine system disorders	(17)	Cellular movement	(17)
Gene expression	(17)	Tumor morphology	(17)
Cellular developments	(17)	Cell morphology	(17)
Inflammatory response	(17)	Cell signaling	(17)
Cell adhesion	(17)	Hematological system , development and functions	(17)
Calcium signaling pathway	(17)	Connective tissue development	(17)
PPAR Signaling pathway	(17)	Toll like receptor signaling pathway	(17)
Fatty acid metabolism	(17)		

For showing the correlation between RA and hot/cold temperaments in one study, CD_4^+ T cell RNA was extracted and gene expression measured by microarray. If the rate of cold pattern gene expression to the hot pattern was more or less than 1.2, it is taken as differential gene expression. The result showed that four genes are highly expressed in patients with cold pattern and 21 genes have lower expression in cold pattern. These genes involved in different networks and four of these networks were found that can be used to classify rheumatoid arthritis patients' pattern. These networks appear to be involved in small G protein signaling pathways (TIAM1), fatty acid metabolism (ALOX5) and T cell proliferation that is higher in patients with the hot pattern. By having this knowledge rheumatoid arthritis patients could be divided into different groups to receive different therapies. The cold pattern shows a better response to biochemical therapy than the hot pattern (16). Rheumatoid arthritis patients that classified into the cold/hot group have different sign and symptoms and their pain relief with different medication. As the previous study on RA, patients with cold pattern show a better response to biochemical combination therapy than hot patients. Another study tries to investigate the relation between gene expression profiling to CD_4^+ T cell and hot/cold pattern in RA patients. For this purpose, microarray procedure has been done on CD_4^+ T cell RNA of 20 RA patients. Then protein-protein interaction and all networks have been surveyed, and 29 genes have found in related to hot/cold pattern in RA. Seven of these genes expressed significantly higher in cold pattern. Besides this, four connected regions were detected in protein-protein interaction investigation. The cold pattern region is involved toll-like receptor signaling pathway and in the heat pattern cell signaling pathway, cell adhesion molecular, PPAR signaling pathway, fatty acid metabolism, so all these different results in pattern differentiation and this differentiation affect the efficacy of biochemical therapy (Table 2) (17).

Another study on rheumatoid arthritis based on Neuroendocrine immune (NEI) shows other results. Neuroendocrine-immune (NEI) has an essential role in information exchanges between these three systems that are important in lots of

Table 3. Genes that involved in determining hot and cold.

Cold				Hot			
Gene name	**ID**	**MIM**	**Ref**	**Gene name**	**ID**	**MIM**	**Ref**
EGR1	1958	128990	(16)	TIAM1	7074	600687	(16)
LPAAT-THETA	84803	610958	(17)	ALOX5	240	152390	(16)
COL6A1	12833		(17)	H2AFX	3014	601772	(16)
ENST00000256367	23508		(17)	LIG1	3978	126391	(16)
TLR4	21898		(17)	CCL3L3	414062	609468	(17)
SPECC1	92521	608793	(17)	HLA-DRB4	3126		(17)
				CABLES1	91768	609194	(17)
				APOA1	335	107680	(17)
				KLHL4	56062	300348	(17)
				IGHD	380797		(17)
				SPP1	6696	166490	(17)
				WWOX	51741	605131	(17)
				PSCD4	27128	606514	(17)
				DNHD3	146754	603333	(17)
				C1QTNF6	114904	614910	(17)
				RASD1	51655	605550	(17)
				RBM21	64852	610641	(17)

physical and pathological process. Etiopathogenesis of many diseases such as RA has come from NEI abnormality. Rheumatoid arthritis is caused by HLA_DRB1 gene and some environmental factors and differentiated as cold/hot. Omics at the micro level and TCM phenotype based clinical practice at the macro level bridged by NEI system cause promotion and deeper the perception of complex disease mechanism. Changes in neurotransmitters, hormones or cytokine by NEI in micro level regulate body response to environmental stress and disease phenotype in macro level. So every disorder in micro level results in hot/ cold CM syndrome that is macro level. For investigating the bridging action of NEI system between micro and macro level, one cold syndrome has been chosen and then the expression of 10 genes was analyzed and 25 differentially expressed gene by $P<0.005$ in T-test are identified. The gene-gene and protein-protein interaction's investigation show that differentiated gene has a closer relationship to hot/cold NEI gene than any other gene. More investigation shows that there is a relationship between NEI and energy metabolism that itself lead to cold symptoms show that abnormal communication between NEI cold/hot genes leads to TCM cold syndrome (7).

Based on what Cheng GuoPeng said, for a manifestation of illness if there is thirst, preferences of cold beverage, food and feels vexed, if urine is scant and radish, if the stool is dry-bound and pulse is rapid, it is hot. If there is no thirst, preference of hot beverage, copious clear urine, semi-liquid stool and loose pulse, it is the cold pattern. When an illness develops to the stage of extreme hot/cold, there will be a false manifestation that contradicts with exact nature of the illness. For example, extreme yin (cold) can convert into dry heat, so there is interior cold with exterior heat, called true cold-false heat (7).

There were 61 and 57 genes respectively in hot and cold temperaments patients, these genes with their ID shown in table 3. By looking at the Venn chart by FunRich database, there is no common gene between hot and cold, but it does not mean that there is not any similarity in their functions.

By entering our genes in FunRich and Panther database, we study them from different

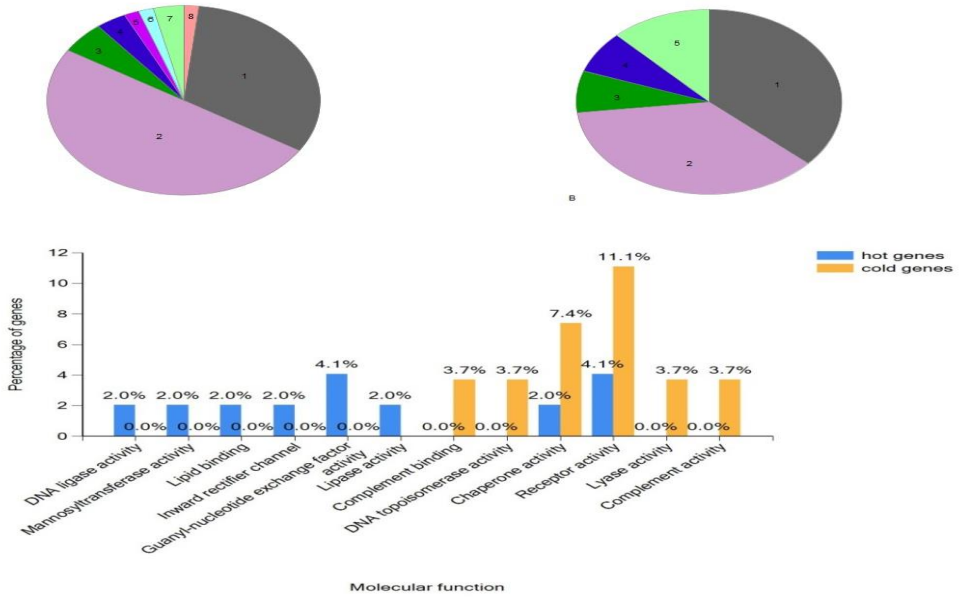

Figure 2. Molecular Function analysis in a) hot gene and b) cold gene by Panther and c) by FunRich.

Hot gene: 1.binding 32% 2.catalyzing activity 50% 3.receptor activity 5.4% 4.signaling activity 3.6% 5.molecular structure 1.8%. 6.translation process activity 1.8%. 7.carrier activity 3.6%. 8.antioxidant activity 1.8%
Cold gene : 1.binding 36.6% 2.catalyzing activity 36.6% 3.receptor activity 7.3% 4.signaling activity 7.3% 5.carrier activity 12.2%.

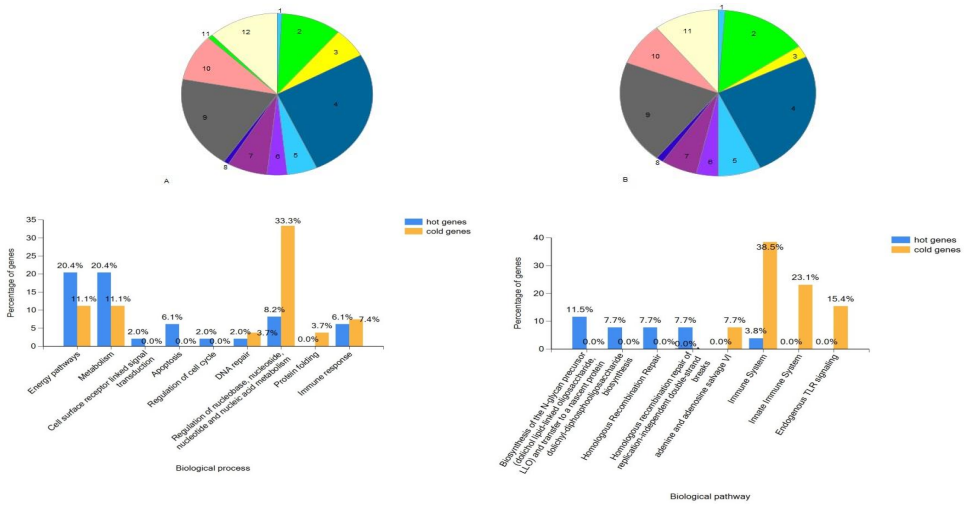

Figure 2. Biological processes analysis in a)hot gene and b)cold gene by Panther and c)by FunRich.

Hot gene: 1.cellular adhesion 0.8% 2.biological regulation 10.2% 3. Cellular component organization or biogenesis 5.9% 4.cellular process 26.3% 5.developmental process 5.1% 6.immune system process 3.4% 7.localization 6.8% 8.locomotion 0.8% 9.metabolic process 18.6% 10.multicellular organismal process 9.3% 11.reproduction 0.8% 12.response to stimulus 11.9%
Cold gene: 1.cellular adhesion 1.2% 2.biological regulation 14.3% 3. Cellular component organization or biogenesis 2.4% 4.cellular process 25% 5.developmental process 7.1% 6.immune system process 3.6% 7.localization 6% 8.locomotion 1.2% 9.metabolic process 20.2% 10.multicellular organismal process 8.3% 11. .response to stimulus 10.7%.

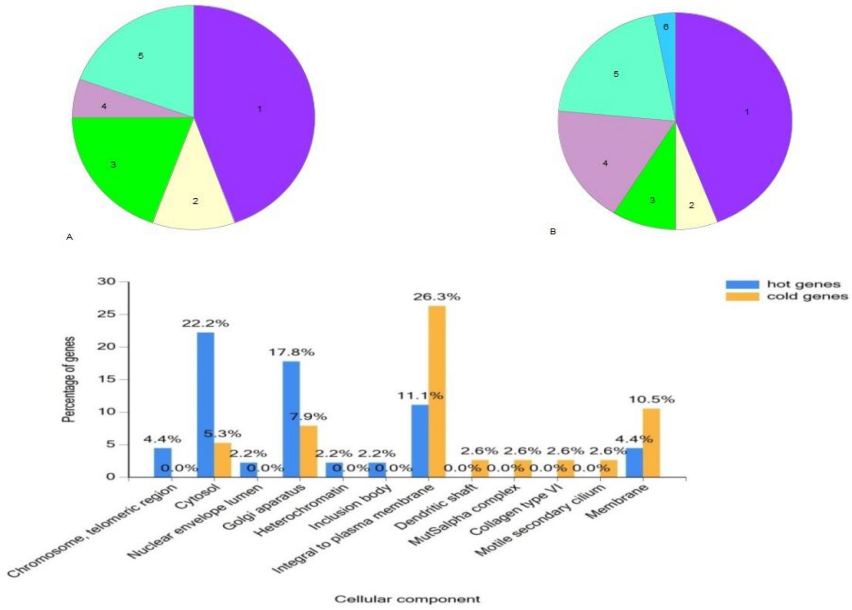

Figure 3. Cellular component analysis in a)hot gene and b)cold gene by Panther and c)by FunRich.

Hot gene: 1.cell part 44.4% 2.extracellular matrix 11.1% 3.macromollecular complex 19.4% 4.membrane 5.6% 5.organelle 19.4% Cold gene: 1.cell part 44.1% 2.extracellular matrix 5.9% 3.macromollecular complex 8.8% 4.membrane 17.6% 5.organelle 20.6% 6.synapse 2.9%.

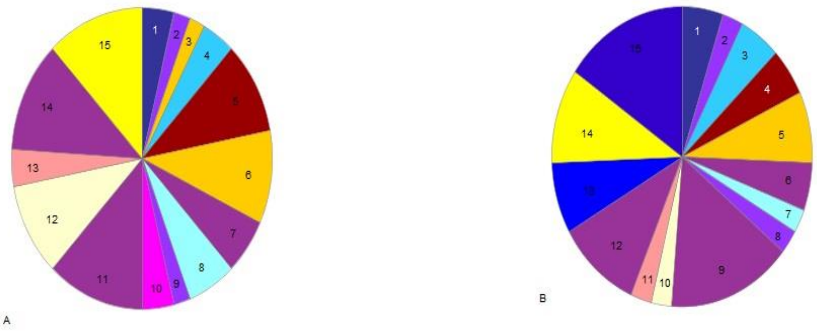

Figure 4. Protein class analysis in a)hot gene and b)cold gene by Panther.

Hot gene: 1.Calcium binding protein 4% 2.chaperon 2% 3.cytoskletal protein 2% 4.defense/immunity protein 4% 5.enzyme modulator 10% 6.hydrolase 10% 7.isomerase 6% 8.ligase 6% 9.lyase 2% 10.membrane protein 4% 11.nucleic acid binding 12% 12.oxidoreductase 10% 13.receptors 4% 14.signaling molecule 12% 15.transferase 12%
Cold gene: 1.Calcium binding protein 5.1% 2.chaperon 2.6% 3.defense/immunity protein 5.1% 4.enzyme modulator 5.1% 5.hydrolase 7.7% 6.isomerase 5.1% 7..ligase 2.6% 8.lyase 2.6% 9.nucleic acid binding 15.4% 10.oxidoreductase 2.6% 11.receptors 2.6% 12.signaling molecule 10.3% 13.transcription factors 7.7% 14.transferase 10.3% 15.transporter 15.4% .

aspects and also compare hot and cold genes in different aspects. These analyses by FunRich and Panther showed in figure 1 to 5.

These genes have different functions based on Uniprot database that can divide into different category. The functions classified into 5 categories, including immune response (121 functions) , cell cycle (140 functions) , energy and metabolism (69 functions) , development and differentiation (48 functions) and signaling (52 functions).

In table 4 to 8 the cold/hot ratio for each function are expressed. This ratio shows the number of cold genes with specific function relative to the number of the hot gene with the same function. The essential functions are those that have significant differences between two temperaments that

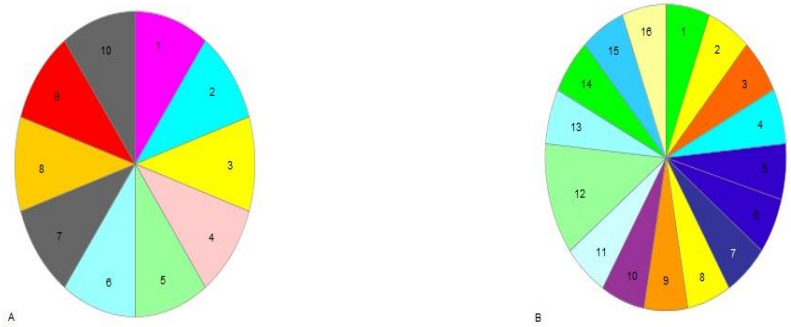

Figure 5. Pathway analysis in a)hot gene and b)cold gene by Panther.

Hot gene: 1.apoptose signaling pathway 10% 2.GABA receptor II signaling 10% 3.GNRH receptor hormone pathway 10% 4.huntington disease 10% 5. Inflammation mediated by chemokine and cytokine signaling pathway 10% 6.intengrin signaling pathway 10% 7.mannose metabolism 10% 8.parkinson disease 10% 9.RAS pathway 10% 10.TGF-beta signaling pathway 10%
Cold gene: 1. Alzheimer disease – amiloide pathway 5.9% 2. Alzheimer disease – presenilin pathway 5.9% 3.angiogenesis 5.9% 4. Angiotensin II-stimulated signaling through G proteins and beta-arrestin 5.9% 5.blood coagulation 5.9% 6.CCKR signaling map 5.9% 7.glycicolysis 5.9% 8.GNRH receptor hormone pathway 5.9% 9. Heterotrimeric G-protein signaling pathway-Gi alpha and Gs alpha mediated pathway 5.9% 10. Heterotrimeric G-protein signaling pathway-Gq alpha and Go alpha mediated pathway 5.9% 11. Hypoxia response via HIF activation 5.9% 12. Inflammation mediated by chemokine and cytokine signaling pathway 11.8% 13.integrin signaling pathway 5.9% 14. Metabotropic glutamate receptor group III pathway 5.9% 15.toll receptor signaling pathway 5.9% 16.VEGF Signaling pathway 5.9%.

Table 4. Function contributing in immune response and their cold/hot ratio.

Function	Ratio*
innate immune response	7:5
inflammatory response	4:6
defense response to bacterium	1:2
positive regulation of inflammatory response	1:2
positive regulation of interleukin-6 production	2:1
defense response to Gram-positive bacterium	2:1
negative regulation of apoptotic process	1:2
neutrophil chemotaxis	0:3
positive regulation of interleukin-8 production	1:1
programmed cell death	1:1
regulation of immune response	1:2
antibacterial humoral response	1:1
cellular response to interleukin-1	1:1
chemokine activity	1:1
complement activation	2:0
complement activation, alternative pathway	2:0
complement activation, classical pathway	1:1
cytokine-mediated signaling pathway	1:1
cytolysis	2:0
defense response to fungus	0:2
defense response to Gram-negative bacterium	1:1
defense response to virus	1:0
detection of virus	1:0
immune response	0:2
killing of cells of other organism	0:2
MHC class I protein complex binding	1:1
monocyte chemotaxis	0:2
negative regulation of neuron apoptotic process	0:2
negative regulation of T cell proliferation	1:1
positive regulation of apoptotic process	0:2
positive regulation of interferon-alpha biosynthetic process	1:0
positive regulation of interferon-beta biosynthetic process	1:0
positive regulation of interferon-beta production	1:0
positive regulation of interferon-gamma biosynthetic process	1:0
positive regulation of interleukin-12 production	1:0
positive regulation of T cell proliferation	1:1
positive regulation of tumor necrosis factor production	1:0
positive regulation of type III interferon production	1:0
regulation of apoptotic process	1:1
T cell proliferation	1:1
viral process	1:1
acute inflammatory response	0:1
adaptive immune response	0:1

Continued Table 4.

antifungal humoral response	1:0
antigen binding	0:1
antigen processing and presentation, endogenous lipid antigen via MHC class Ib	1:0
antigen processing and presentation, exogenous lipid antigen via MHC class Ib	1:0
antimicrobial humoral response	0:1
B cell receptor signaling pathway	0:1
B-1 B cell homeostasis	1:0
cellular defense response	0:1
cellular hyperosmotic response	0:1
cellular response to antibiotic	1:0
cellular response to drug	1:0
cellular response to interferon-gamma	0:1
cellular response to oxidative stress	0:1
cellular response to tumor necrosis factor	0:1
chemotaxis	1:0
connective tissue replacement involved in inflammatory response wound healing	1:0
cytokine secretion	0:1
detection of bacterium	1:0
endogenous lipid antigen binding	1:0
eosinophil chemotaxis	0:1
humoral immune response	1:0
immune response-inhibiting cell surface receptor signaling pathway	0:1
immunoglobulin receptor binding	0:1
interleukin-1-mediated signaling pathway	0:1
leukocyte migration	1:0
leukotriene biosynthetic process	0:1
leukotriene production involved in inflammatory response	0:1
lymphocyte chemotaxis	0:1
mast cell activation	0:1
MHC class I protein binding	0:1
MHC class Ib protein binding	0:1
MHC class Ib protein binding, via antigen binding groove	0:1
natural killer cell mediated immunity	0:1
negative chemotaxis	0:1
negative regulation of antigen processing and presentation	0:1
negative regulation of B cell activation	1:0
negative regulation of cytokine secretion involved in immune response	0:1
negative regulation of fibroblast apoptotic process	0:1
negative regulation of humoral immune response mediated by circulating immunoglobulin	1:0
negative regulation of immune response	0:1
negative regulation of inflammatory response	0:1
negative regulation of interleukin-1 beta secretion	0:1

Continued Table 4.

negative regulation of interleukin-6 biosynthetic process	1:0
negative regulation of intrinsic apoptotic signaling pathway in response to osmotic stress	0:1
negative regulation of macrophage chemotaxis	1:0
negative regulation of T cell differentiation in thymus	1:0
negative regulation of thymocyte apoptotic process	1:0
negative regulation of tumor necrosis factor-mediated signaling pathway	0:1
neuron apoptotic process	1:0
phagocytosis, engulfment	0:1
phagocytosis, recognition	0:1
positive regulation of B cell activation	0:1
positive regulation of central B cell tolerance induction	1:0
positive regulation of defense response to virus by host	1:0
positive regulation of extrinsic apoptotic signaling pathway	0:1
positive regulation of extrinsic apoptotic signaling pathway in absence of ligand	0:1
positive regulation of immune system process	1:0
positive regulation of innate immune response	1:0
positive regulation of interleukin-1 alpha secretion	1:0
positive regulation of interleukin-1 beta secretion	1:0
positive regulation of lymphocyte apoptotic process	1:0
positive regulation of regulatory T cell differentiation	0:1
positive regulation of T cell mediated cytotoxicity	1:0
positive regulation of T cell tolerance induction	0:1
positive regulation of tumor necrosis factor-mediated signaling pathway	0:1
protein antigen binding	0:1
regulation of complement activation	1:0
regulation of complement activation	1:0
regulation of killing of cells of other organism	1:0
response to interleukin-1	0:1
response to oxidative stress	1:0
response to yeast	1:0
T cell costimulation	0:1
T cell differentiation	1:0
T cell homeostasis	1:0
T cell receptor signaling pathway	0:1
T cell selection	1:0
virus receptor activity	0:1
wound healing	1:0
xenobiotic metabolic process	0:1

ratio=number of gen contributing in cold temperament vs. hot temperament.

Table 5. Function contributing in cell cycle and their ratio in cold and hot pattern.

Function	Ratio
DNA binding	8:3
transcription factor activity, sequence-specific DNA binding	7:2
positive regulation of transcription from RNA polymerase II promoter	5:2
negative regulation of transcription from RNA polymerase II promoter	4:3
negative regulation of transcription, DNA-templated	3:4
DNA repair	3:3
positive regulation of transcription, DNA-templated	3:3
transcription, DNA-templated	4:2
poly(A) RNA binding	1:4
histone binding	2:2
positive regulation of gene expression	2:1
protein oligomerization	3:1
regulation of transcription, DNA-templated	3:1
sequence-specific DNA binding	4:0
cell cycle	1:2
DNA duplex unwinding	1:2
double-strand break repair	2:1
double-strand break repair via homologous recombination	2:1
gene expression	0:3
negative regulation of cell proliferation	1:2
positive regulation of cell proliferation	1:2
regulation of transcription from RNA polymerase II promoter	2:1
regulation of transcription from RNA polymerase II promoter in response to hypoxia	2:1
transcriptional activator activity, RNA polymerase II core promoter proximal region sequence-specific binding	3:0
ATP-dependent 3'-5' DNA helicase activity	1:1
cell division	0:2
chromatin binding	1:1
chromatin silencing	0:2
double-strand break repair via nonhomologous end joining	0:2
double-strand break repair via synthesis-dependent strand annealing	2:0
double-stranded RNA binding	1:0
mRNA polyadenylation	1:1
peptidyl-prolyl cis-trans isomerase activity	1:1
post-embryonic development	0:1
regulation of gene expression	2:0
regulation of mitotic cell cycle	1:0
regulation of mitotic cell cycle	0:1
spermatogenesis	1:1
transcription corepressor activity	0:2
transcription factor binding	1:1
transcription regulatory region DNA binding	1:1
transcription regulatory region sequence-specific DNA binding	2:0
ubiquitin protein ligase binding	1:1
5'-nucleotidase activity	0:1

Continued Table 5.

aminoacyl-tRNA editing activity	0:1
angiogenesis	1:0
annealing helicase activity	1:0
ATP-dependent DNA helicase activity	1:0
ATP-dependent helicase activity	1:0
bubble DNA binding	1:0
cell proliferation	0:1
chromatin assembly	1:0
chromatin organization	0:1
chromosome organization	1:0
damaged DNA binding	0:1
DEAD/H-box RNA helicase binding	0:1
DNA biosynthetic process	0:1
DNA damage checkpoint	0:1
DNA dealkylation involved in DNA repair	0:1
DNA double-strand break processing	1:0
DNA ligase (ATP) activity	0:1
DNA ligase activity	0:1
DNA ligation	0:1
DNA packaging	1:0
DNA recombination	1:0
DNA replication	1:0
DNA replication-dependent nucleosome assembly	1:0
DNA strand elongation involved in DNA replication	0:1
DNA strand renaturation	1:0
DNA topoisomerase type I activity	1:0
DNA topological change	1:0
double-stranded methylated DNA binding	0:1
endothelial cell proliferation	0:1
erythrocyte maturation	0:1
four-way junction helicase activity	1:0
global genome nucleotide-excision repair	0:1
glomerular mesangial cell proliferation	1:0
guanyl-nucleotide exchange factor activity	0:1
helicase activity	1:0
histone acetylation	0:1
intestinal epithelial cell maturation	1:0
meiotic cell cycle	0:1
meiotic nuclear division	1:0
microtubule-based movement	0:1
mismatch repair	0:1
mitotic cell cycle	0:1
mitotic G2 DNA damage checkpoint	1:0
mRNA transcription from RNA polymerase II promoter	1:0
negative regulation of cell death	0:1

Continued Table 5.

negative regulation of cell division	1:0
negative regulation of DNA recombination	1:0
negative regulation of G1/S transition of mitotic cell cycle	0:1
negative regulation of telomerase activity	0:1
negative regulation of telomere maintenance via telomerase	0:1
nucleosome assembly	0:1
nucleotide binding	0:1
nucleotide-excision repair	0:1
nucleotide-excision repair, DNA gap filling	0:1
Okazaki fragment processing involved in mitotic DNA replication	0:1
positive regulation of cytolysis	1:0
positive regulation of DNA repair	0:1
positive regulation of DNA replication	0:1
positive regulation of DNA strand elongation	0:1
positive regulation of endothelial cell proliferation	1:0
positive regulation of epithelial cell proliferation	1:0
positive regulation of helicase activity	0:1
positive regulation of mitotic cell cycle	1:0
positive regulation of neuroblast proliferation	1:0
positive regulation of pri-miRNA transcription from RNA polymerase II promoter	1:0
positive regulation of telomerase activity	0:1
positive regulation of transcription from RNA polymerase II promoter in response to hypoxia	1:0
protein folding	1:0
regulation of cell cycle	0:1
regulation of cell proliferation	1:0
regulation of gene expression by genetic imprinting	0:1
regulation of mRNA stability	0:1
regulation of transcription from RNA polymerase II promoter in response to oxidative stress	1:0
regulation of translation	1:0
removal of RNA primer involved in mitotic DNA replication	0:1
RNA polymerase II core promoter proximal region sequence-specific DNA binding	1:0
RNA polymerase II core promoter sequence-specific DNA binding	1:0
RNA polymerase II regulatory region sequence-specific DNA binding	1:0
RNA polymerase II transcription coactivator activity	0:1
siRNA binding	0:1
SNARE complex disassembly	0:1
snRNA processing	0:1
telomerase inhibitor activity	0:1
telomere maintenance via recombination	0:1
transcription from RNA polymerase II promoter	1:0
transcription, DNA-template	1:0
transcription, DNA-templated	0:1
translation	0:1
translation factor activity, RNA binding	0:1
translation initiation factor activity	0:1

Continued Table 5.

translational initiation	0:1
tRNA (cytosine) methyltransferase activity	0:1
tRNA aminoacylation for protein translation	0:1
tRNA methylation	0:1

Table 6. Function contributing in energy and metabolism and their ratio in cold and hot.

Function	Ratio
ATP binding	5:11
cellular protein metabolic process	2:6
small molecule metabolic process	2:4
positive regulation of GTPase activity	1:3
ATPase activity	1:2
cellular lipid metabolic process	2:1
glycolytic process	1:2
glycolytic process	0:2
response to estrogen	0:3
response to glucose	1:2
response to hypoxia	1:2
response to nutrient	0:3
activation of NF-kappaB-inducing kinase activity	1:0
activation of protein kinase activity	1:1
carbohydrate metabolic process	1:1
cellular response to hypoxia	1:1
collagen metabolic process	2:0
glucocorticoid metabolic process	0:2
GTP binding	0:2
GTPase activity	0:2
lactate metabolic process	1:1
nucleobase-containing small molecule metabolic process	1:1
proteolysis	2:0
response to hyperoxia	0:2
small molecule metabolic process	2:0
transporter activity	2:0
triglyceride catabolic process	1:1
acetylcholine receptor binding	1:0
adenosine metabolic process	0:1
anion transmembrane transport	1:0
arachidonic acid metabolic process	0:1
ATP metabolic process	0:1
ATPase activator activity	1:0
ATPase activity, coupled	0:1
bile acid metabolic process	1:0
canonical glycolysis	0:1
carbon-carbon lyase activity	1:0
cardiolipin metabolic process	0:1

Continued Table 6.

cellular metabolic process	0:1
cholesterol metabolic process	0:1
DNA metabolic process	0:1
elastin metabolic process	1:0
gluconeogenesis	1:0
glucose 6-phosphate metabolic process	0:1
glucose metabolic process	0:1
glutamine metabolic process	0:1
inositol metabolic process	0:1
insulin secretion	0:1
leukotriene metabolic process	0:1
lipid metabolic process	1:0
lipoprotein metabolic process	0:1
lipoxin metabolic process	0:1
mannose metabolic process	0:1
NAD metabolic process	0:1
negative regulation of reactive oxygen species metabolic process	1:0
nucleotide metabolic process	0:1
organophosphate metabolic process	1:0
phosphate-containing compound metabolic process	0:1
phosphatidylcholine metabolic process	0:1
phospholipid metabolic process	1:0
purine nucleobase metabolic process	1:0
pyrimidine nucleobase metabolic process	0:1
pyrimidine nucleoside metabolic process	0:1
pyruvate metabolic process	0:1
reactive oxygen species metabolic process	1:0
retinoid metabolic process	0:1
small molecule metabolic process	0:1
steroid metabolic process	0:1
UDP-N-acetylglucosamine metabolic process	0:1

Table 7. Function contributing in development and differentiation and their ratio in cold and hot.

Function	Ratio
osteoblast differentiation	1:2
brain development	1:1
cerebral cortex development	1:1
dendrite development	1:1
negative regulation of osteoclast differentiation	1:0
post-embryonic development	1:0
adrenal gland development	0:1
biomineral tissue development	0:1
cartilage development	1:0
cell differentiation	1:0
central nervous system development	1:0

Continued Table 7.

cerebellum development	0:1
chorion development	1:0
dopaminergic neuron differentiation	1:0
embryonic placenta development	1:0
endodermal cell differentiation	1:0
epidermis development	1:0
epithelial cell differentiation involved in mammary gland alveolus development	1:0
epithelium development	1:0
erythrocyte differentiation	0:1
exocrine pancreas development	1:0
glomerular parietal epithelial cell development	1:0
heart development	0:1
in utero embryonic development	1:0
lung epithelium development	1:0
metanephric part of ureteric bud development	1:0
negative regulation of dendritic spine development	0:1
nervous system development	0:1
neuron differentiation	0:1
neuron projection development	1:0
oligodendrocyte differentiation	1:0
optic nerve development	0:1
peripheral nervous system development _	1:0
positive regulation of erythrocyte differentiation	1:0
positive regulation of lung ciliated cell differentiation	1:0
positive regulation of neuron differentiation	0:1
post-embryonic organ development	0:1
regulation of cell differentiation	1:0
regulation of dendritic cell differentiation	0:1
regulation of keratinocyte differentiation	1:0
retina development in camera-type eye	1:0
retina vasculature development in camera-type eye	1:0
skeletal muscle cell differentiation	1:0
skeletal system development	1:0
spermatid differentiation	1:0
substantia nigra development	0:1
syncytiotrophoblast cell differentiation involved in labyrinthine layer development	1:0
ventricular system development	0:1

Table 9. Function contributing in signaling and their ratio in cold and hot.

Function	Ratio
signal transduction	4:1
apoptotic process	1:3
cell surface receptor signaling pathway	3:2
G-protein coupled receptor signaling pathway	1:4

Continued Table 8.

post-translational protein modification	1:4
protein phosphorylation	3:2
extrinsic apoptotic signaling pathway	2:1
synaptic transmission	2:2
transmembrane signaling receptor activity	2:1
response to electrical stimulus	2:1
sensory perception of pain	1:2
signal transduction	0:3
apoptotic signaling pathway	1:1
axon guidance	1:1
cell-cell signaling	1:1
cytokine-mediated signaling pathway	1:1
I-kappaB kinase/NF-kappaB signaling	1:0
necroptotic signaling pathway	1:0
regulation of ARF protein signal transduction	1:1
signal transduction by protein phosphorylation	1:1
stress-activated protein kinase signaling cascade	1:1
toll-like receptor 3 signaling pathway	1:0
toll-like receptor 4 signaling pathway	1:0
toll-like receptor signaling pathway	1:0
TRIF-dependent toll-like receptor signaling pathway	1:0
Wnt signaling pathway	1:1
B cell receptor signaling pathway	0:1
blood vessel endothelial cell migration	0:1
BMP signaling pathway	1:0
calcium-mediated signaling using intracellular calcium source	0:1
ephrin receptor signaling pathway	0:1
Fc receptor mediated inhibitory signaling pathway	0:1
Fc-epsilon receptor signaling pathway	0:1
Fc-gamma receptor signaling pathway involved in phagocytosis	0:1
hypoxia-inducible factor-1alpha signaling pathway	1:0
integrin-mediated signaling pathway	0:1
interferon-gamma-mediated signaling pathway	0:1
intrinsic apoptotic signaling pathway by p53 class mediator	0:1
intrinsic apoptotic signaling pathway in response to hydrogen peroxide	1:0
ionotropic glutamate receptor signaling pathway	1:0
negative regulation of adrenergic receptor signaling pathway involved in heart process	1:0
negative regulation of Wnt signaling pathway	0:1
neurotrophin TRK receptor signaling pathway	0:1
nitric oxide mediated signal transduction	0:1
positive regulation of chemokine-mediated signaling pathway	1:0
positive regulation of Ras protein signal transduction	0:1
positive regulation of Rho protein signal transduction	0:1
Rac protein signal transduction	0:1
regulation of Cdc42 protein signal transduction	0:1

Continued Table 8.

toll-like receptor signaling pathway	1:0
type I interferon signaling pathway	1:0
Wnt signaling pathway	0:1

can help us reach an overall conclusion.

3.10. Drugs and compounds

In all traditional medicine all over the world, there is a belief that besides Body, illness and medicine, all foods and compounds have temperaments too; it means it effects on the temperament of the human body.

In one study for investigation these effects, after determining of each person's temperament, In the second stage, people divided to two groups (cold & warm) and two subgroups and a randomized, double-blind crossover trial designed. Some take thyme (*Zataria multiflora* Boiss) and some take sumac (*Rhuscoriaria, anacardiaceous*). Their BMR, peripheral and central body temperature, heart rate, blood pressure and also adrenalin, noradrenalin and cortisol level measured. After six day washout period, thyme and sumac were given to another subgroup; then these parameters were measured again. So the effect of food on people's temperament has been investigated (14).

Another study shows that medicine with hot or cold properties affects hemostasis of the body. People with hot temperament has a more active sympathetic system and less parasympathetic system and adrenal corticosteroid and adrenal activities and also a higher rate of deviation of the immune system to T-helper2. So in this study the effect of hot and cold seeds on FT3, FT4, T3, T4 and glucocorticosteroid (the main reason of thermogenesis) and VMA (Vanillylmandelic acid) considered, for this purpose 3 hot and 3 cold plants have been chosen, then they give to Wistar male rat and their urine and blood collected to measure the VMA in urine and thyroid hormone in blood. Anise and fennel seeds as hot plant decrease the FT3 serum level and Ajowan (hot) increase T3 level in serum. Fennel seed also increases FT4 and Anise, fennel and Ajowan and watermelon increase T3. There is no significant difference in corticosterone level after 24 hours, but there is a significant increase in watermelon and pumpkin group after seven days. Regarding VMA, there is no significant difference after 24 hours, but after seven days fennel seed increases and cucumber decreases this in urine. It is supposed that this increase in thyroid hormone is because of increased generation of T4 in the thyroid gland and also increasing the diversion of T4 to T3 decrease in the amount of FT3 and FT4 is also because of increasing the binding of the hormone o thyroid binding protein

Table 9. Function contributing in energy and metabolism and their ratio in cold and hot.

Hot	Ref	Cold	Ref
Decrease in FT3 by fennel and anise family in 24 hours	(4)	Increase in corticosterone by pumpkin and watermelon family in 7 days	(4)
Increase in T3 by ajowan family in 24 hours	(4)	Decrease in urine VMA by cucumber in 7 days	(4)
Increase in FT4 by fennel	(4)	The decrease in skin temperature by coconut water	(5)
increase in T3 by fennel, anise and ajowan in 7 days	(4)		
Increase in Urine VMA by fennel in 7 days	(4)		
Increase in NLF% by coconut water	(5)		
Increase in LF/HF ratio by coconut water	(5)		
Increase in HF% by ginger tea	(5)		
Increase in nHF by ginger tea	(5)		
Increase in Capillary RBC velocity by coconut water	(5)		
Increase in glucose uptake	(18)		
Increase in NE release	(18)		

(Table 9) (4).

TCM believed that herbal medicine has different properties (hot/cold/warm/cool) which are essential in prescribing them too. These characteristics of food originating from the reaction of the body to them. Based on TCM, cold food clear hot, remove toxic substances and nourish Yin. In contrast, hot property food warms up the interior dispel cold and supports yang (14).

Chinese believe that the property of hot/cold herbal medicine should be investigated depended on organic human response than to their chemical compound. For investigating the pattern of HM, 300 commonly used HM were collected and their indication, component and properties were listed, then divided to hot/cold by three primary TCM references. Then their human protein target was performed in PubChem. The main component of every HM was fragmented into specific chemical molecule fragment then classified based on their structure. Then their function and toxicity are defined too, and canonical pathway analysis was performed. 16 networks imported for ten cold HM and 23 networks for hot HM. Some of the most critical networks are cell cycle, cellular growth and proliferation and development pathway. Cold properties specific networks are cellular assembly and organization, cellular movement, tumor morphology, cell morphology, cell signaling, hematological system, connective tissue development. Hot properties specific networks are cancer, endocrine system disorders, gene expression, cellular development and inflammatory response (Table 3). The top 5 networks of hot and cold properties HM were combined and then compared with each other. Three of them do not show significant differences that show cold/hot properties HM share common bio-function to a large degree in canonical pathway analysis. There are 11 pathways for hot HM and only 1 for cold HM that is RNA signaling. IPA also shows the active molecule in each canonical pathway. These are RAN, KPNBL for the cold pattern, and PRKACA, PRKCA, PRKCB, PRKCD, PRKCE, PRKCG, PRKD1, TLR4, TLR7, 8,9, MAPK1, RPS6KAI, RPS6KA3, JAK2, for hot pattern HMs. Beside of these the hepatotoxicity, cardiotoxicity and nephrotoxicity of the 20 HM were analysis in IPA. It shows that in hepatotoxicity cold HM has an intensive effect on hepatitis and the cold one on liver cirrhosis and both on hepatocellular carcinoma. In cardiotoxicity, also, some general effect cold pattern affects pulmonary hypertension and nephrotoxicity, both groups affect kidney failures, renal nephritis and renal necrosis (cold pattern HM has a stronger effect) after a chemical fragment of each HM component. It is observed that long-chain alkene was found only in cold ones. Benzoheterocycles has a high frequency and azotic group (related to its hepatotoxicity) that shows that chemical structure is more related to toxicity that bioactivities (19). Other studies show a relation between chemical ingredients such as mineral and organic compounds of food and their nature. Some studies show that nutritional content of most elements is higher in hot/warm food than cold/cool foods. The iron content of cool/cold food is higher whereas the content of manganese is lower. The protein content of cold/cool foods is lower, so the protein content of food is related to its nature. This is as similar as carbohydrate. For showing the relation between the content of food and its nature food with clearly stated nature selected and divided into cold/hot/neutral. Then their content values derived from China food composition database include water, energy, protein, fat, carbohydrate, *etc.* Significant differences were found for water, energy, fat, protein, cholesterol, carotene, retinol, vitamin C, Zinc, selenium among cold, neutral and hot group. Going from cold to hot, the amount of energy and selenium increased whereas the content of water, carotene and retinol decreased.

Concerning the increase in fat, carbohydrate and selenium by one unit, the probability of hot nature of increased by 1.69 times, 1.443 for cold and 1.438 for neutral nature. So fat, carbohydrate and selenium-related to hot nature and iron and copper related to cool (20).

Some study refers cold/hot pattern in the term to oxidation/antioxidant ion in modern western medicine and PGE2 production by macrophage cell line. Another study tries to find a suitable method to identify the attributes of food ingredients by investigating the relationship between this and physiological signals of the body. For this purpose, some patients selected and divided into

hot/cold constitution groups then ginger tea and coconut water have given to patients and Tongue diagnosis, heart rate variability (HRV), time and frequency domain, skin and axillary temperature, capillary RBC velocity of NFM were measured before and after eating the samples. Every patient does this procedure three times for ginger, coconut, and water as blank, with a one-week interval. After measuring this variation in every physiological signal, there are no differences in baseline signals of hot/cold patients, except HR that is lower in cold constitution patients. After taking samples, there is no difference in axillary temperature, but skin temperature significantly reduced in cold patients who take coconut water than those taking ginger tea. nLF%(Sympathetic activity) and LF/HF ratio (Sympathovagal ratio) increased in a hot patient, who take coconut water rather than those taking ginger tea. Also, the HF and nHF% of hot patients increased after taking ginger tea. The capillary RBC velocity of hot patient increased after taking ginger tea and decreased in cold patients after taking coconut water. Capillary RBC velocity of hot patients increased with taking hot food. It means that hot food raised yang in hot person and vice versa. Also, cold food increased sympathetic activity that results in vasoconstriction (5).

Another research on the property of herbs tries to investigate the effect of cold/cool/warm/hot herbs on oxidative stress, glucose uptake and norepinephrine release from a cultured nerve cell. For this purpose, the N9 cell cultured and herbs extract added to the cells in 96 well culture plates. After that, glucose uptake, oxidative stress and epinephrine release have measured. Most of the herb extract have a cytotoxic effect on N9 cells but not in the concentration lower than 1 mg/ml. After adding H2O2 to induced oxidative stress, 18 herbs show protective capacity that is dose dependent in 16 of them and dose-independent in 2 of them. Except two of these 18 herbs, others show this protective effect by reversing the reduction of superoxidase dismutase activity induced by H_2O_2. Beside this, hot pattern herbs stimulate glucose uptake, but cold pattern herb does not affect tor reduce its uptake. Also, seven of 15 hot herbs increased NE release, but none of the cold herbs show such this effect. The protective effect of these herbs against oxidative stress in the neural cell can use to treat neurological diseases such as Alzheimer and Parkinson (18).

4. Discussion

By reviewing 118 identified genes for cold and hot temperament and examining the functions associated with these genes and their proteins, there was a significant difference in some of these functions between the two temperaments.

As gene and protein databases show, in the immune processes hot genes play more roles in inflammatory and chemotactic processes, apoptosis and response to bacteria and fungus, while the cold genes are more responsible for the inherent immunity of the body, the complement system activity and cell lysis, as a subject that has been proven and illustrated in previous studies, individuals with different temperaments show different responses to biochemical treatments (16). In processes associated with cell cycle, cold genes cause increased DNA binding and more transcription from a specific DNA sequence and hot genes cause negative transcriptional regulation, binding to Poly (A) RNA, gene expression and repair and, in a significant amount, cause cell division.

Among the processes involved in energy and cellular metabolism, hot genes are observed more; these genes are involved in metabolic processes and ATP activity. The only functions that cold genes dominate on hot genes are the protein lysis processes, the collagen metabolism, and the activity of carriers and transporters.

In the identified functions related to the development and differentiation of the cells, it can be said that the cold and hot genes are somewhat equivalent and these types of functions are not superior to any of the temperaments. In signaling processes, apoptotic processes, G-protein receptors signaling pathway and posttranslational protein changes and pain sensation are more in warm temperament, on the other hand, transmission pathway of receptors at the cell surface, the proteins phosphorylation, and extrinsic apoptosis signaling pathway is more in the cold. Investigations conducted by Panther and FunRich in molecular functions show that half of the activities in hot temperament are related to catalytic activity,

which is also seen in lower amounts in cold temperament. However, in hot temperament, activities such as translation-related activities and anti-oxidant activities are seen, that do not exist in cold temperament. In the cold temperament, there is also activity related to complement system, which is not seen in the hot temperament. Among the biological processes, hot genes are more involved in the processes of energy production and metabolism, while cold genes play a role in nucleotide and nucleobase processes.

Cold and hot genes are present almost identically in different parts of the cell, and only the extent of this presence varies in different parts, For example, hot genes are present in the cellular part, organelles such as cytosol and Golgi's body and macromolecular complexes, while cold genes are present in the cell portions and membrane more. Among the protein classes in which warm and cold genes are involved, one can see the similarity of protein classes between the two groups. The only difference in these categories is involvement of cold genes in a high amount of protein carriers that are not seen in hot genes. Unlike protein classes, there is a significant difference in the pathways where cold and hot genes interfere. In this category, hot genes are involved in the pathway of Parkinson's disease, Huntington and apoptosis, and cold genes are effective in different pathways of creating Alzheimer's, blood coagulation and angiogenesis. Indeed, a more in-depth and more comprehensive review of this concept can guide us to the cause of occurrence of certain diseases in some individuals and the following ways of preventing it.

Since the toxicity and side effects of synthetic drugs is high there is a high tendency toward traditional medicine among people nowadays but there is a high amount of ancient sources of this medicine that is still a mysterious and there is doubt about their content, so it is essential to put more effort on decryption of it and be more familiar with these medicines all over the world. One of the critical theory behind the traditional medicine of every country is that every person with specific body composition and properties need a specific treatment as he/she is also more susceptible to certain diseases. Something that called "personalized medicine" nowadays and does not exist till now. Up to day medicine is "standards of care" that means something that is best for general no matter who you are and medications are same for all the person with identical signs and symptoms, so the medications may work for some patients but not for many others. Today we know that it is because of the unique genetic makeup of each person and also due to environmental factors that affect everyone's life in a specific way. Therefore we need pattern identification so we can take a step toward personalized medicine and also a more sufficient and satisfactory treatment for a disease.

Conflict of Interest

None declared.

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