

원저

## The Structural Characteristics of the Active Ingredients in Several "Hot and Warm" Herbal Medicine

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### ABSTRACT

韓藥의 溫熱性藥의 成分과 化學的 特性에 關한 研究

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韓藥의 效能은 藥性에 의해 分類되고 疾病을 治療하며 豫防하는 作用을 한다. 그러나 藥性 理論의 文獻과 臨床研究는 비교적 많지만 상대적으로 實驗研究는 일부분에 불과하여 效能을 立證하는데 어려움이 많다. 이에 著者는 溫熱性藥들이 지니고 있는 有效 成分들을 調査하고 이 溫熱性藥에 含有되어 있는 有效 成分들의 構造의인 特性과 化學的인 共通點을 찾아 溫熱性藥의 分類에 대한 一般的인 基準을 提示하고자 하였다.

그 결과 각각의 熱性藥과 溫性藥들이 含有하고 있는 有效 成分간의 構造의인 共通點을 찾아내었으며 構造의인 共通點으로부터 다음과 같은 結論을 얻었다.

1. 熱性藥 중에서 강한 毒性을 나타내는 附子和 草烏의 효능을 나타내는 有效 成分들은 C19-diterpenoid alkaloid과 C20-diterpenoid alkaloid 계열의 構造를 지닌 化合物들로 構成되어 있다.

이 디테르펜 알칼로이드(diterpene alkaloid)들의 경우 고리의 構造가 aconitane(1), hetisan(16)과 7,20-cycloveatchane(17)의 基本骨格을 지니고 있으며, 이 두 가지 基本構造의 共通點은 A 고리에 질소를 포함한 2-azabicyclo-[3.3.1]-nonanyl 의 부분구조를 갖고 있으며, 이 부분 구조는 자연계에 존재하는 tropane alkaloid들의 基本構造와 유사하다.

Tropane alkaloid 들은 중추신경계에 작용하는 藥物들로 알려져 있으며, tropane alkaloid 는 일반적으로 anatoxin a(171) 와 같이 강한 毒性을 나타내며, 附子和 草烏가 지니고 있는 강한 毒性은 바로 2-azabicyclo-[3.3.1]-nonanyl 構造에 기인하는 것으로 추정할 수 있다.

2. 肉桂에 주성분으로 含有되어 있는 cinncassiol(47) 化合物들은 분자 내에 bicyclo-[4.3.0]-nonanyl 과 bicyclo-[3.3.0]-octanyl 의 기본 혹은 부분 구조를 지니고 있다.

3. Cinncassiol(47) 化合物들은 강한 抗菌力을 보이고 있는데, cinncassiol(47) 化合物들이 지니고 있는 구조적인 특성인 bicyclo-[4.3.0]-nonanyl과 bicyclo-[3.3.0]-octanyl의 기본 혹은 부분 고리구조는 sesquiterpenoid 化合物들과 diterpenoid 化合物들중에서 많이 발견되며, 이러한 構造를 지니고 있는 sesquiterpenoid 化合物과 diterpenoid 化合物들도 좋은 抗菌力을 보이고 있다. 이러한 共通된 構造上의 類似點이 抗菌力을 나타내는 지표로서 활용 가능성이 기대된다.

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4. 溫性藥의 경우, 白芷의 coumarin(39) 化合物들과 furocoumarin(61) 化合物들, 乾薑의 gingerol(87), shogaol(93), gingerdiol(95) 등과 capsaicin(102), 麻黃의 ephedrine(124) 系列 化合物들, 細辛의 methyleugenol(136)과 asaricin(137)의 構造에서 發見할 수 있는 共通的인 요소는 phenolic 또는 methoxyphenyl 의 공통구조를 지니고 있다. 溫性藥의 유효성분들은 공통적으로 phenolic aromatic 化合物를 含有하고 있다.

따라서, 熱性藥과 溫性藥은 主成分들의 分布가 각기 다르며, 毒性을 나타내는 熱性藥은 2-azabicyclo-[3.3.1]-nonanyl 構造를 지니고 있고, 肉桂와 같은 抗菌力을 지니는 藥物은 bicyclo-[3.3.0]-octanyl 또는 bicyclo-[4.3.0]-nonanyl의 構造를 지닌다.

白芷, 麻黃, 細辛 등에서 볼 수 있듯이 溫性藥은 benzene 構造를 含有하는 phenolic aromatic 化合物들이 주종을 이룬다.

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Key Word : 有效成分, 溫熱性藥, 構造的인 共通點, 毒性, 抗菌力, effective elements, hot and warm herbal medicine, structural similarity, poisonous characteristics, antibiotic capability

## I. Introduction

A systematic theory has been developed from <<Shen Nong Ben Cao Jing>> which separates the properties into cold, hot, warm, cool and equal as it illustrates different methods to treat various diseases.

"Warm" herbal medicine and "hot" herbal medicine have the following effects inside the body: warms the interior to dispel cold, dispels pathogenic factors from the exterior of the body, supplements fire of the vital gate to invigorate Yang, restores Yang from collapse, invigorates the pulse-beat, promotes blood flow, and removes blood stasis.

It has been observed that "warm" and "hot" herbal medicine control the synthesis and the separation of the material being transmitted by the sympathetic nervous system having a stimulation effect. Previous research has not clearly revealed the characteristics of "Ki-Mi-Rhon" or the theories on properties and flavors of drugs. Therefore, the author has conducted research on the effective elements contained in the "warm" herbal medicine and tried to identify the chemical similarities between

the elements which are part of the medication that brings out the "warm" quality. This, in turn, has been used to present a general standard.

The following medications have been selected for research: "hot" herbal medicine compounds including "Bu-Ja(ACONITI LATERALIS PREPARATA RADIX)," "Cho-Oh(ACONITI ICILIARE TUBER)," "Yuk-Gae(CINNAMONI CORTEX)" and "Kun-Kang(ZINGIBERIS RHIZOMA)"; "warm" herbal medicine compounds including "Baek-Ji(ANGELICAE DUHURICAE RADIX)," "Ma-Hwang (EPHEDRAE HERBA)" and "Se-Shin(ASARI HERBA CUM RADICE)." These compounds contained in the "warm" and "hot" herbal medicine have been researched in the literature.

After careful analysis of these effective compounds, it was found that "Bu-Ja" and "Cho-Oh" of the "hot" herbal medicine contain compounds effective for central nervous system. They have a similar structure to 2-azabicyclo-[3.3.1]-nonanyl. Cinnassiol(47) and other effective compounds are contained in "Yuk-Gae" and they have a common partial structure with bicyclo-[4.3.0]-nonanyl and bicyclo-[3.3.0]-octanyl.

These structures, which are present in naturally occurring compounds, display antibiotic effects.

In "warm" quality medication, there are common structural points between "Baek-Ji," "Ma-Hwang" and "Se-Shin." This research shows that those common structures are present.

This study is believed to have its significance in classifying oriental medication characteristic into an index by cold, hot, warm, cool and equal, and also to provide important information for new medication development in the future.

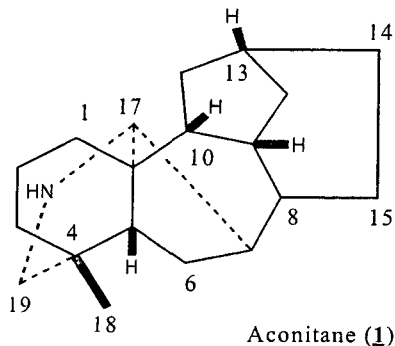
## II. Main Text

[1] "Hot" herbal medicine

(1) "Bu-Ja"

(ACONITI IATERALIS PREPARATA RADIX)

"Bu-Ja" is made from processing the roots of *Aconitum carmichaeli* DEBX, which is part of Ranunculaceae family and is classified as perennial herbal plant. "Bu-Ja" possesses the following properties: hot-nature, poisonous, and the taste that is bittersweet. In general, it contains chemical compounds, C19 and C20 diterpene alkaloids.



The poisonous characteristics in "Bu-Ja" comes from aconitine(2), and aconitine(2)

has a basic structure of aconitane(1), which is part of diterpene alkaloid having a skeletal base of four rings. Lipoaconitine(20) is a lipoalkaloid but is different from aconitine(2) by having the following substituted groups in place of an acetyl group on C-8: palmitoylcarboxy, stearoylcarboxy, linoleoylcarboxy, oleoylcarboxy, linolenoylcarboxy. The seed of "Bu-Ja" after roasting can be separated into aconitine(2), mesaconitine(3), hypaconitine(4), talatisamine(5), isotalatisidine(6), 14-acetyltalatisamine(7), karacolone(8), neoline(9), jesaconitine(24), lipoaconitine(20), lipohypaconitinine(21), lipomesaconitine(22) and lipodeoxyaconitine(23). In addition, benzoylaconine(26), benzoylhypaconine(27) and benzoylmesaconine(28) have been isolated. Lipoaconitine(20), lipohypaconitinine(21), lipomesaconitine(22), lipodeoxyaconitine(23) and jesaconitine(24) possess less poisonous characteristic than aconitine(2) and mesaconitine(3). Lipomesaconitine(22) manifest anti-inflammatory and has a soothing effect.

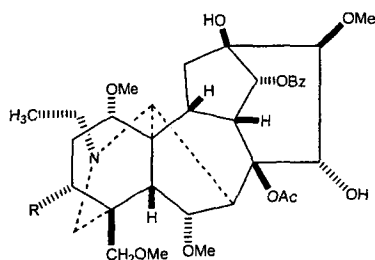
Coryneine chloride (29), isolated from the root, possesses an aromatic compound resembling phenethylamine different from the former basic structure of aconitane(1) chemical compounds and is known for its ability to contract the speed and the size of an isolated guinea pig atria. Salsolinol(30), a chemical compound of isoquinoline alkaloid order, has been isolated from root of "Cheuk-Sang," and this compound has the ability to work as a heart stimulant and also as anti-hypertension effects.

"Bu-Ja" has a medical function of anti-inflammatory effects, while aconitine(2) can suppress increased blood vessel osmosis, edema formation of the heel and granulated tissue formation. The extraction from the root can be used as an insulin suppository and to reduce the blood sugar

level during a cramp. Aconitane A, B, C and D have properties, which manifest a reduction of the sugar level during a cramp.

(2) "Cho-Oh" (ACONITI ICILIARE  
TUBER)

"Cho-Oh" is part of Ranunculaceae family and is the same genus as *Aconitum ciliare* DC., a perennial herb. The properties of this medication is "hot" and poisonous, and the taste is extremely spicy. "Cho-Oh" has a high poisonous characteristic, but it has both a soothing effect as well as muscle relaxation effect. It is similar to "Bu-Ja" by having diterpene alkaloid chemical compounds as its major components and being part of the aconitane(1) order. Isolation of main components of "Cho-Oh" gives aconitine(2), mesaconitine(3), hyaconitine(4) and 3-deoxyaconitine(25). Also neoline(9), songorine(18), beiwutine(31), bullatine A(32) and bullatine C(33) have been isolated, along with newly found chemical compounds: nagarine(34), penduline(35) and 3-acetylaconitine(36). The newly identified beiwutine(31) in "Cho-Oh" displays similar structure as mesaconitine(3), but has an extra hydroxyl group on C-10. This compound has an analgesic capabilities.



Aconitine (2): R=OH  
3-Deoxyaconitine(25): R=H  
3-Acetylaconitine(36): R=OAc

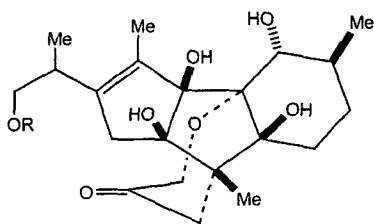
The quantity of alkaloids from extracting root of "Bu-Ja" differed from the extraction

time and place of specimen collection. The total alkaloid amount usually recorded 0.08~0.79%, of which aconitine(2) took 0.03~0.06%, mesaconitine(3) took 0.1~0.6% and hyaconitine(4) took 0.02~0.2%.

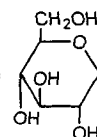
(3) "Yuk-Gae" (CINNAMONI CORTEX)

"Yuk-Gae" is part of Laureceae family and is the dried bark of "Yuk-Gae" *Cinnamomum cassia* PRESL, an evergreen arbor plant. Its nature is "hot" and innocuous, and taste is bittersweet. It has an oil component of 1~2%, main extraction ingredient of cinnamaldehyde(37) that takes up 75~90%, and is known to have the following other components: cinnamic acid(38), coumarin(39), *b*-sitosterol(40), choline(41), protocatechuic acid(42), vanilic acid(43) and small amount of syringic acid(44). It is also reported that the leaf contains hydroxycinnamic acid(45) and hydroxybenzoic acid(46).

From the aqueous extraction of "Yuk-Gae," there are ten diterpene compounds, which show anticomplement activity. These kinds of diterpene compounds are called cinnacassiol. Cinnacassiol compounds are formed from four chains, and from the differences in frame structure, cinnacassiol compounds can be separated into lactone, ketal and diketone forms. From the extraction of a bark with anti-allergic effect, cinnacassiol D1(52) and cinnacassiol D2(53) have been isolated.



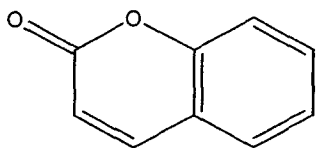
Cinnacassiol A(47): R=H  
Cinnacassiol A O-b-D-glucopyranoside: R=



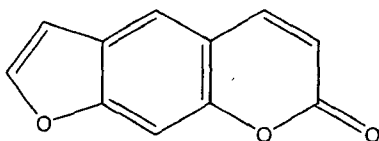
[2] "Warm" herbal medicine

(1) "Baek-Ji"(ANGELLICAE  
DUHURICAE RADIX)

"Baek-Ji" is part of the Umbelliferae family and is from the dried root of 2~3 year old herbal plant, which is the same genus as *Angelica dahurica* BENTH. et HOOK. Its nature is "warm" and innocuous, and it has a spicy taste. In the root of "Baek-Ji," there are many kinds of coumarin(39) and furocoumarin(61) derivatives. Coumarin(39) is a benzopyrane compound that has been formed from the fusion of benzene and pyrane. It has been reported that four kinds of coumarin compounds have been isolated from "Baek-Ji," and they are scopoletin(62), 7-demethylsuberosin(63), 6-methoxy-7-(methyl-2-butenyloxy)coumarin(64) and cedrelpsin(65).



Coumarin (39)



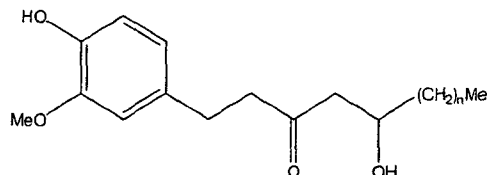
Psoralen (66)

There are two chemical structures in the nature. One is psoralen(66) where furan structure is linear and connected to coumarin(39), which has a chemical name of furo[3,2-g][1]benaopyran-7-one. The other is angelicin(67) with a chemical

name, furo[3,2-h]-1-benzopyran-2-one, that has furan fused with C-7 and C-8 of coumarin(39). The furocoumarin(61) identified in "Baek-Ji" has confirmed to be of psoralen(66) order of compounds. Beside coumarin(39) and furocoumarin(61) orders of compounds, one can find lactone order of compounds in "Baek-Ji".

(2) "Kun-Kang" (ZINGIBERIS  
RHIZOMA)

"Kun-Kang" is part of the Ginger family (Zingiberaceae) and is made from dried root stock of perennial herbal plant, *Zingiberis officinale* ROSC. Its nature is "hot" and innocuous, and its taste is spicy. Of the main component, gingerol(87-92) is known to manifest the spicy taste, and it is part of a phenolic compound. There is long side chain emerging from the carbonyl group, which is in the para-position of the hydroxyl group. Its chemical name is 1-(4-Hydroxy-3-methoxyphenyl)-5-hydroxyalkan-3-one, and the side chain has a S(+) spatial structure, and depending on the length of the side chain, there exist six kinds of same family derivatives.



[3]-Gingerol (87): n=1  
[4]-Gingerol (88): n=2  
[5]-Gingerol (89): n=3  
[6]-Gingerol (90): n=4  
[8]-Gingerol (91): n=6  
[10]-Gingerol (92): n=8

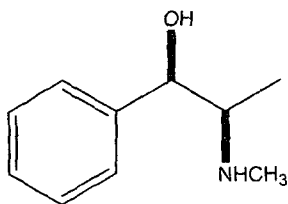
Of the compounds that have been isolated from "Kun-Kang," there was a spicy component, capsaicin(102), which is a major component in pepper. In the oil component of "Kun-Kang," there are many

types of terpene compounds present. There are also sesquiterpene order of compounds, which all have gone through hydration for its double fusion. Besides the above compounds, asparagine, pipercolic acid, glutamic acid and asparagin acid are also present.

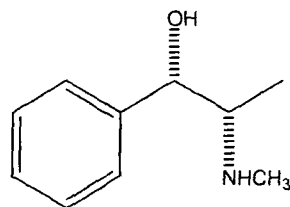
(3) "Ma-Hwang" (EPHEDRAE HERBA)

"Ma-Hwang" is made from dried initial stock substance and is obtained from *Ephedra sinica* STAPF, *E. intermedia* SCHRENK et C.A. MEY or *E. equisetina* BGE, all small perennial herbal shrub, which is part of *Ephedraceae* family. Its nature is "warm" and the taste is quite spicy and a bit bitter.

The major component of "Ma-Hwang" is ephedrine(124), an alkaloid, which has been well known for over 100 years, and its chemical name is  $\alpha$ -[1-(methylamino)-ethyl]-benzenemethanol. This compound has two asymmetric carbons, and there are four stereo isomers. Four of the isomers are split into two types of diastereomers: (-)- and (+)-ephedrine(124); (+)- and (-)-pseudoephedrine(125). (-)-ephedrine(124) and (+)-pseudoephedrine(125) from "Ma-Hwang" are natural compounds with 1R, 2S erythro stereo structure, while (+)-ephedrine(124) and (-)-pseudoephedrine(125) are non-natural compounds obtained through synthesis.



(-)-ephedrine (124)



(+)-ephedrine (124)

(4) "Se-Shin" (ASARI HERBA CUM RADICE)

"Se-Shin" is made from the dried root and herb of a perennial herbal plant, *Asarum sieboldii* MIQ and plants from the same genus of *Aristolochiaceae* family. Its nature is "warm" and innocuous, and the taste is spicy.

In the root of "Book-Se-Shin," same genus as "Jok-do-ri" herb, there are approximately 1.9~3% oil component, and from this component, compounds were identified by gas chromatography-mass spectrometer. The main element is methyleugenol(136) (There are approximately 50% of oil component in the root of "Jok-do-ri" herb). The other compounds were  $\alpha$ -pinene(103),  $\beta$ -pinene(104), myrcene(107), 1,8-cineole(109), asaricin(137), eucarvone(138), elemicin(139), higenamine(140), croweacin(141),  $\alpha$ -thujene(142), terpinen-4-ol(143),  $\alpha$ -terpineol(144), safrole(145) and myristicin(146).

### III. Consideration

After conducting chemical research on these substances, the following results were obtained.

(1) "Bu-Ja" (ACONITI LATERALIS PREPARATA RADIX) and "Cho-Oh" (ACONITI CILIARE TUBER)

The main element of "Bu-Ja" and "Cho-Oh" is aconitine(2) with C19-diterpenoid

alkaloid structure with base frame of aconitane(1) as described in the main text section. C19-diterpenoid alkaloid can be divided into two shapes, aconitane(1) and heteratisine. Of the two, aconitane(1) form can be divided into three shapes. The first type is similar to aconitine(2) with no substituted group on C-7 and just has a hydrogen attached to it. The second type has oxidation on C-7 and consists of compounds such as lycocotinine(147), browniine(148), dilcosine(149) and dictyocarpine(150). The third type has double joint in between C-8 and C-15, and falacotinine(151) and mithaconitine(152) are part of this type.

Atisine(155) has bicyclo-[2.2.2]-octanyl structure in its molecule and is relatively innocuous in comparison to aconitine(2), and it is known to have an effect on the cardiovascular system. Veatchine(156) compounds possess bicyclo-[3.2.1]-octanyl form in the molecule that is unique, and they are very toxic, and for the medical effects, they induce shortness of breath, convulsions and hinders respiratory activities.

C19-diterpenoid alkaloid compounds such as aconitine(2) from "Bu-Ja" and "Cho-Oh" along with C20-diterpenoid alkaloid compounds found in plants of Ranunculaceae and Garryaceae families, have a 2-azabicyclo-[3.3.1]-nonanyl form in common after analysis of structural characteristics of A-ring in these compounds. This type of structure is commonly found in tropane alkaloid and is similar to 9-azabicyclo-[4.2.1]-nonanyl form with nitrogen and 8-azabicyclo-[3.2.1]-octanyl form.

From tropane alkaloids, the simplest and the most representative compound is anatoxin a(171), isolated from *Anabaena glos-aquae* (Cyanophyceae), a type of alga. This compound is known as the "very fast

death" factor and is recorded to have been used as a weapon by African tribal people on the arrow tips. It is a deadly poison and paralyzes the central nervous system.

#### (2) "Yuk-Gae" (CINNAMONI CORTEX)

Cinnamaldehyde order of compounds, isolated from "Yuk-Gae" is diterpenoid order and fragrant chemical compounds. If the structure of diterpenoid compounds are analyzed, then they can be separated into two structural frames: cinnassiol A(47) with "5-membered ring + 5-membered ring + 6-membered ring" and cinnassiol D(52) with "5-membered ring + 6-membered ring + 5-membered ring." If these two compounds are separated into bicyclic compounds, then they are split into two types: bicyclo-[3.3.0]-octanyl and bicyclo-[4.3.0]-nonanyl. As discussed in the main text, cinnassiol(47) has a medical potency of being antibacterial, antibiotic, anti-allergy and causes vasodilation.

#### (3) "warm" herbal medicine

There are many types of coumarin(39) isolated from "Baek-Ji," and they are aromatic compounds in the benzopyrane order where benzene and pyrane are fused together. Furocoumarin(61) compounds have been found to be the main components in "Baek-Ji."

The main component of "Kun-Kang" is gingerol(86), which has a spicy taste. Gingerol(86) has a chemical name of 1-(4-hydroxy-3-methoxyphenyl)-5-hydroalk an-3-one, and it is of phenolic aromatic compound, a benzene structure with hydroxyl group attached. It is known that through biosynthesis of phenylalanine, variety of gingerol(87) can be produced. There are compounds other than gingerol(87) known to display the spicy taste of "Kun-Kang," and they are shogaol(93) and zingerone(94) and have a

phenolic aromatic structure that is similar to gingerol(87) form. Of the components isolated and identified from "Kun-Kang," capsaicin(102) is known to be a main part of a pepper, acting as a spicy element. There is an amide connection in this molecule and is a phenolic aromatic compound with a hydroxyl group and a benzene ring.

Ephedrine(124), a main component of "Ma-Hwang," has been known for 100 years and has a chemical name  $\alpha$ -[1-(methylamino)-ethyl]-benzenemethanol. There are 2 asymmetric carbons and 4 stereo isomers. The 4 stereo isomers are separated into 2 types of diastereomer and are called ephedrine(124) and pseudoephedrine(125). With its chemical names, one can find out that they are aromatic compounds.

Methyleugenol(136) is a main component of "Se-Shin" and is part of aromatic compounds with substituted groups attached to the benzene ring. The main compounds found in "Se-Shin" are categorized chemically as phenolic aromatic base compounds.

From the analysis of the structures of effective compounds in "Baek-Ji," "Kun-Kang," "Ma-Hwang" and "Se-Shin," the compounds are found to be mostly part of the phenolic aromatic compound order.

#### IV. Conclusion

The target of this research has been selected as the effective chemical elements found in the "warm" herbal medicine. These elements were, first, thoroughly researched in the literature. Each of the "hot" herbal medicine and the "warm" herbal medicine have been identified to contain effective elements which have

structural similarities, and these similarities have led to the following implications.

1. There are two effective elements, C19-diterpenoid alkaloid and C20-diterpenoid alkaloid, contained in the "hot" herbal medicine, which display strong poisonous characteristics, usually found in "Bu-Ja" and "Cho-Oh". These two diterpene alkaloids display a basic skeletal frame, ring structure of aconitane(1), hetisan(16) and 7,20-cycloheptane(17). The two elements have a common basic structure with one part comprising of 2-azabicyclo-[3.3.1]-nonanyl containing nitrogen in the A-ring.

This partial structure resembles the basic structure of tropane alkaloid, which exists in nature.

Tropane alkaloids are known as medication used in treating the central nervous system, and they generally manifest same strong poisonous characteristics of anatoxin a(171). Therefore it can be hypothesized that "Bu-Ja" and "Cho-Oh" possess strong poisonous characteristics induced by the 2-azabicyclo-[3.3.1]-nonanyl structure.

2. Main composition of "Yuk-Gae" are cinnassiol(47) chemical compounds, which contains either the base or the partial structure of bicyclo-[4.3.0]-nonanyl and bicyclo-[3.3.0]-octanyl in the molecular structure.

3. Cinnassiol(47) chemical compounds manifest strong antibiotic capability. The basic structure or partial ring structure of bicyclo-[4.3.0]-nonanyl and bicyclo-[3.3.0]-octanyl, which are two unique structural characteristics of cinnassiol(47) chemical compounds, are also commonly found in sesquiterpenoid and diterpenoid chemical



compounds. Sesquiterpenoid and diterpenoid chemical compounds also show good antibiotic capability. There is a high expectation that this mutual structural resemblance can be possibly used as an indicator for elements that manifest antibiotic capability.

4. In the case of "warm" herbal medicine, common structural elements are found to be phenolic or methoxyphenyl structures. These structures are found in the following chemical compounds: coumarin(39) and furocoumarin(61) of "Baek-Ji"; gingerol(87), shogaol(93) and gingerdiol(95) of "Kun-Kang"; ephedrine(124) family of "Ma-Hwang"; methyleugenol(136) and asaricin(137) of "Se-Shin". The effective elements of the "warm" herbal medicine contain phenolic aromatic chemical compounds in common with each other.

Therefore, the distribution of main elements in the "hot" herbal medicine and the "warm" herbal medicine are distinct from one another. The poisonous characteristics manifested by the "hot" herbal medicine contains 2-azabicyclo-[3.3.1]-nonanyl structure. Antibiotic capabilities are displayed by chemicals such as bicyclo-[3.3.0]-octanyl or bicyclo-[4.3.0]-nonanyl structure found in "Yuk-Gae". The "warm" herbal medicine such as "Baek-Ji," "Ma-Hwang" and "Se-Shin" show benzene structure containing phenolic aromatic chemical compounds as its main element.

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