

# 수입식품에 불법첨가한 비아그라 유사체의 규명과 대응



## 수입식품에 불법 첨가한 비아그라 유사체의 규명과 대응

### 홍 무 기

식품의약품안전청 식품안전평가부

New analogues of Sildenafil (Viagra<sup>®</sup>) were identified in the imported Chinese herb drinks, which have been added illegally for affecting penile erectile dysfunction. In order to elucidate the chemical structures of Sildenafil analogues, separation and purification were carried out and followed by analysis of the routine 1D and 2D NMR spectroscopy and FAB mass spectrometry. Based on analytical data one compound was named as Homosildenafil contains ethylpiperazine switched with methylpiperazine of Sildenafil and the other one was called as Hongdenafil contains ethylpiperazine switched with methylpiperazine and acetyl group instead of sulfonyl group of Sildenafil. As results, Homosildenafil and Hongdenafil were put on the list as new inspection items of the imported food for protecting public health in Korea.

## Introduction

- Some food manufacturers have added synthetic drugs or unknown compounds to foods illegally. Moreover, structure-modified compounds could be added, but it is almost impossible to detect them using ordinary laboratory system.
- In this work, I determined the structures of sildenafil-like compounds in the imported foods using HPLC, MS, and NMR.
- The newly synthesized compounds were named as 'homosildenafil' and 'hongdenafil', respectively.
- Ultimately, I want to guard safety of foods from hazardous circumstances.

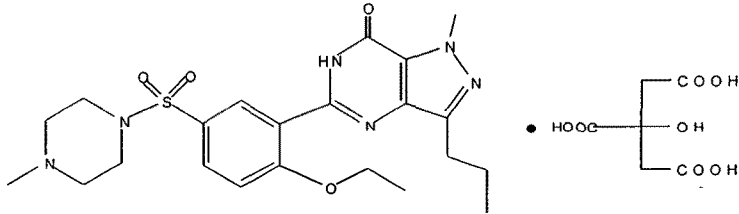


## What is Sildenafil (VIAGRA®)?

- Viagra, an oral therapy for erectile dysfunction, is the citrate salt of sildenafil, a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5).
- Sildenafil citrate is designated chemically as 5-[2-Ethoxy-5-(4-methylpiperazine-1-sulfonyl)-phenyl]-1-methyl-3-propyl-1,6-dihydro-pyrazolo[4,3-d]-pyrimidin-7-one
- The medicinal compound, sildenafil citrate, initially developed to treat patients who had heart disease (angina pectoris). During early clinical trials, an unexpected 'side effect' was discovered : improve and maintain a man's erection.

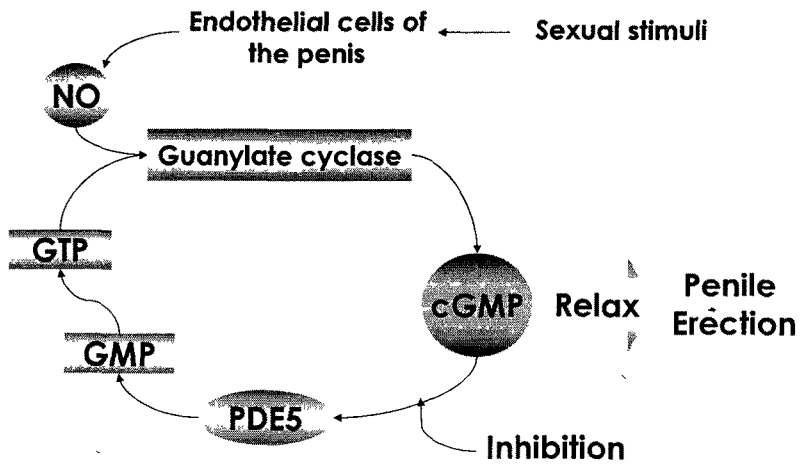


■ Sildenafil citrate is a white to off-white crystalline powder with a solubility of 3.5 mg/ml in water and a molecular weight of 666.7.



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## Mechanism of Action



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## Side Effects

- The most common side effects are headache, flushing of the face, and upset stomach.
- Less common side effects that may occur are temporary changes in color vision (such as trouble telling the difference between blue and green objects or having a blue color tinge to them), eyes being more sensitive to light, or blurred vision.
- In extremely rare instances, men may have an erection that lasts many hours.

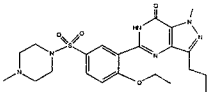

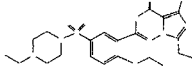


## Medicinal Classification of the Therapies for Impotence

- Testosterone therapy for hypogonadism
- Selective inhibitors of cGMP-specific phosphodiesterase type 5 (PDE5)
  - Sildenafil citrate, Tadalafil, Vardenafil
- Dopamine D<sub>2</sub> receptor stimulator
  - Apomorphine SL (Uprima®, Abbott)
- $\alpha$ -adrenergic antagonist
  - Yohimbine (selective  $\alpha_2$ ), Phentolamine (non-selective)
- Synthetic PGE<sub>1</sub> analogue
  - Alprostadil (intracavernosal and intraurethral)



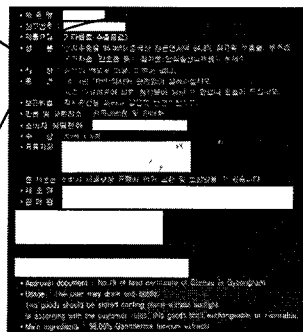
## PDE5 Inhibitors of Drug

Medicine	Chemical structure	Product name	Manufacturer	Side effects
Sildenafil citrate		VIAGRA®	Pfizer	headache, facial flushing, and upset stomach
Tadalafil		Cialis®	Eli Lilly	headache, upset stomach, backache, muscle ache and flushing
Vardenafil		Levitra®	Bayer	headache, flushing, rhinitis and flu syndrome

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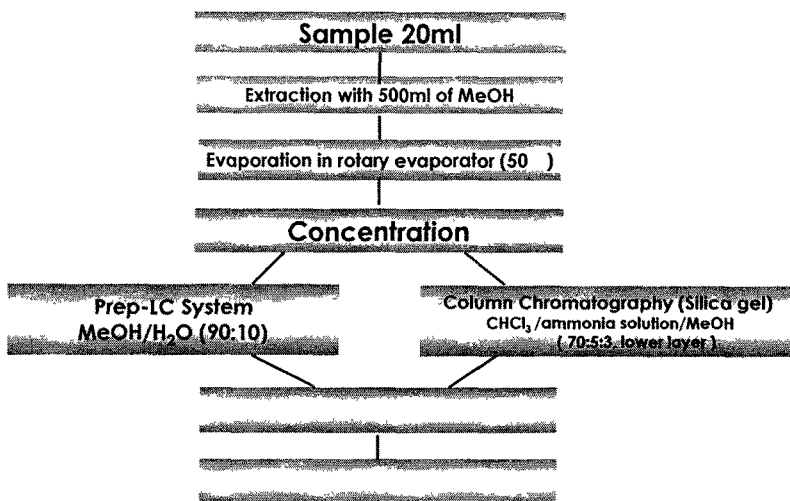
## Labeled Ingredients

**Ganoderma lucidum(영지),  
Eucommia ulmoides(두충),  
Alium tuberosum(부추),  
Lycium chinensis(구기자),  
Glycyrrhiza glabra(감초),  
Poria cocos(복령),  
Royal Jelly(로얄제리),  
Amomum xanthioides(사인)**



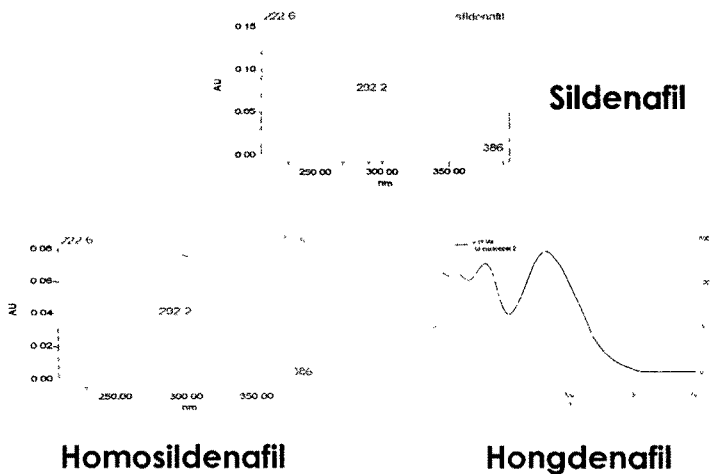
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# Experimental Procedure



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# Comparison of UV Spectra



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## NMR Experiments

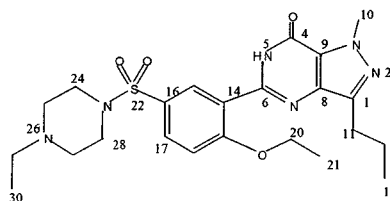
- All NMR experiments were performed on a Bruker Avance 400 spectrometer system (9.4 T) at 298 K.
- The  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, DEPT, COSY, TOCSY, HMQC, HMBC and NOESY spectra were collected in DMSO with TMS as an internal reference.



## Results of 1D NMR

	$\delta$	$\delta$

### Homosildenafil

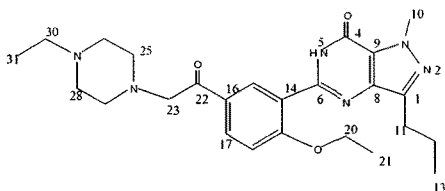


5-[2-Ethoxy-5-(4-ethylpiperazine-1-sulfonyl)-phenyl]-1-methyl-3-propyl-1,6-dihydro-pyrazolo[4,3-d]-pyrimidin-7-one



## Results of 1D NMR

### Hongdenafil



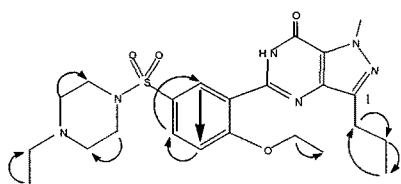
5-[2-Ethoxy-5-[2-(4-ethyl-piperazin-1-yl)-acetyl]-phenyl]-1-methyl-3-propyl-1,6-dihydro-pyrazolo[4,3-d]pyrimidin-7-one

	$\delta$	$\delta$

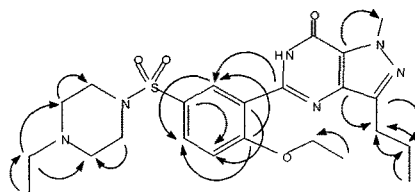
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## Results of 2D NMR

### Homosildenafil



TOCSY

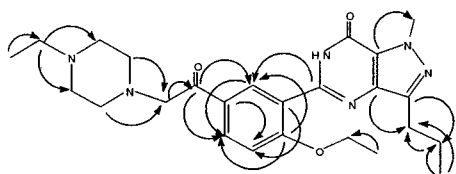


HMBC

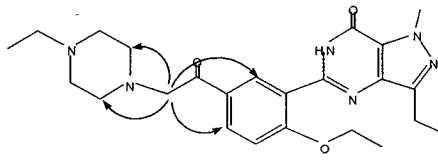
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# Results of 2D NMR

## Hongdenafil



HMBC



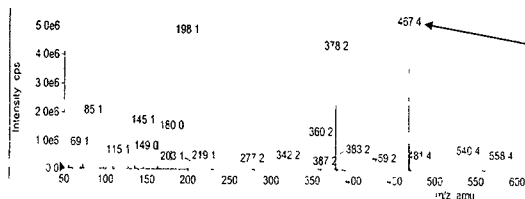
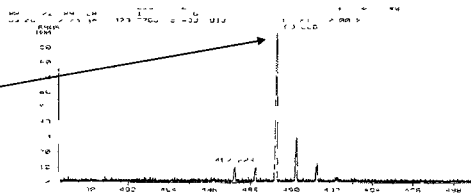
NOESY

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# Comparison of MS Spectra

Homosildenafil  
M.W. 488.2

m/z for [M+H]<sup>+</sup> (C<sub>23</sub>H<sub>33</sub>N<sub>6</sub>O<sub>4</sub>S)  
489 228

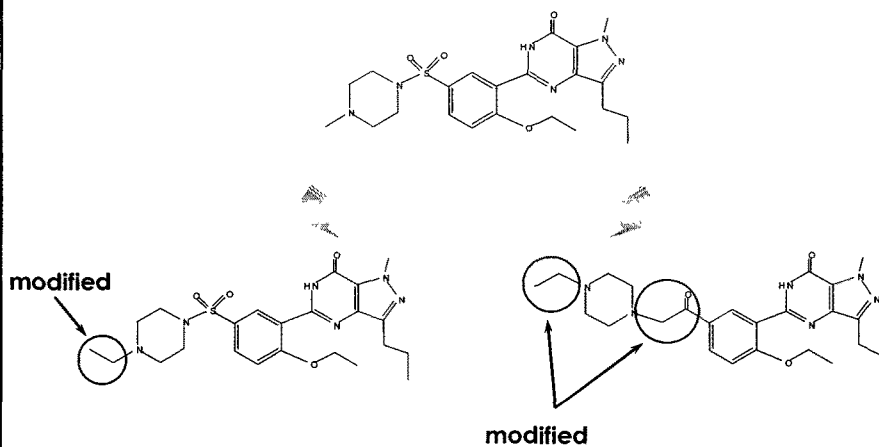


Hongdenafil  
M.W. 466.4

m/z for [M+H]<sup>+</sup> (C<sub>25</sub>H<sub>34</sub>O<sub>3</sub>N<sub>6</sub>)  
467 4

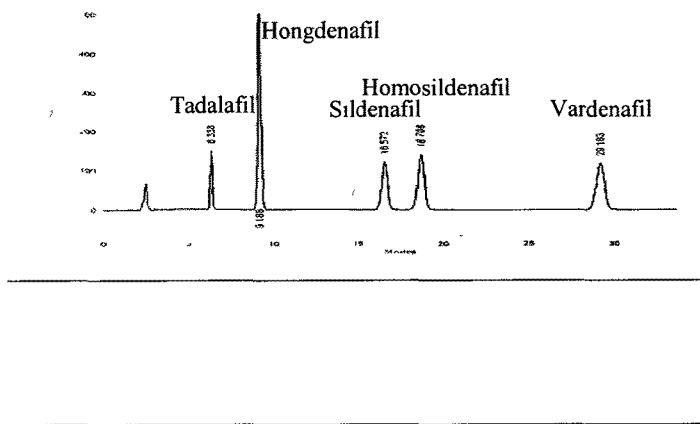
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## Structure Comparison of New Compounds with Sildenafil



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## HPLC Spectra



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# Case #2 – Canada

Health Canada  
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February 15, 2002

2002.09  
February 15, 2002

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## Health Canada warns public not to use Hua Fo They contained sildenafil

OTTAWA - Health Canada is warning consumers not to use Hua Fo tablets, an unapproved herbal product that claims to enhance sexual function. Health Canada analyzed samples of Hua Fo tablets and found that they contained sildenafil. Sildenafil is a drug approved as prescription only for male erectile dysfunction, sold under the brand name Viagra®. Use of sildenafil without medical supervision could cause severe adverse reactions.

Sildenafil should not be used by individuals who are taking any nitrate medication sold by prescription or over the counter. Nitrate medications are commonly used for angina. Concurrent use could result in the development of potentially life-threatening low blood pressure. In extremely rare instances, use of sildenafil could result in penile tissue damage and permanent loss of potency.

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# Case #3 – U.S.A



U.S. Food and Drug Administration



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June 20, 2003 *FDA Talk Paper*

703.48  
June 20, 2003

Media Inquiries: 301-827-6242  
Consumer Inquiries: 888-INFO-FDA

## FDA Public Health Advisory: FDA Warns Consumers Against Taking the Following Dietary Supplements-SIGRA, STAMINA Rx and STAMINA Rx for Women, Y-Y, Spontane ES and Uroprin

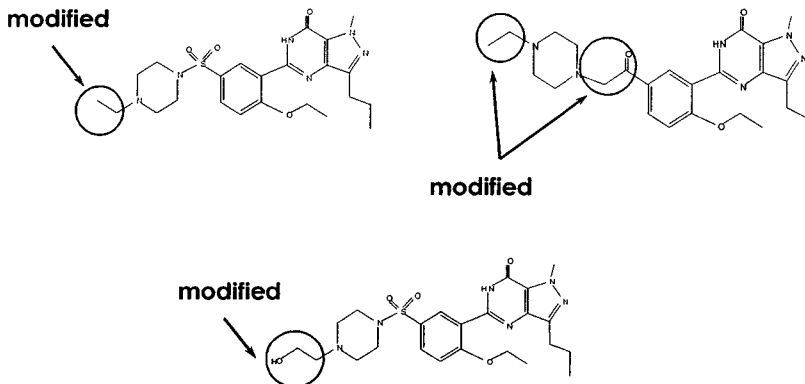
Today, the Food and Drug Administration (FDA) is warning consumers not to purchase or consume the following products: SIGRA, STAMINA Rx and STAMINA Rx for Women, Y-Y, Spontane ES and Uroprin, manufactured by NVE, Inc., in Newton, N.J. and distributed by Hi-Tech in Norcross, Ga. These products, which are being marketed as dietary supplements, actually contain a prescription drug ingredient that poses possible health risks. The products are being sold over the counter and are claiming to increase stamina, confidence and performance.

**tadalafil**

FDA has determined that the products actually contain the prescription strength drug ingredient, tadalafil. Tadalafil is the active ingredient in Cialis, an Eli Lilly product approved in Europe to treat male erectile dysfunction. An interaction between certain prescription drugs containing nitrates (such as nitroglycerin) and tadalafil may cause a drastic lowering of blood pressure. There is real danger that this product may be taken by patients taking nitrates since erectile dysfunction is often a common problem in people with diabetes, hypertension (high blood pressure), hyperlipidemia (high cholesterol), ischemic heart disease and in people who smoke.

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# Analogues of Sildenafil in Food



## Case #4 – Korea

**KFDA** 식품의약품안전청

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**2002.04.23**

**보도/해명자료**

담당부서	식품관리과	작성일	2002.04.23
과장	오균택(吳均澤)	전화번호	380-1515
사무관	사기관 김병태(金秉泰)	전화번호	380-1565
제목	비아그라 성분 및 유사물질등을 식품에 첨가한 압소 등 적발		

<주요내용>

○ 식품의약품안전청은 지속적인 단속에도 불구하고 견본의약품인 구연산실데나필을 식품에 첨가하여 제조 또는 수입 판매한다는 정보가 있어 이에 대한 단속을 실시한 결과

○ 인삼즙류 기타식품 등에 비아그라 성분인 구연산실데나필을 첨가하거나 비아그라 성분과 유사한 물질인 호모실데나필을 원형에서 식품을 제조 수입 판매 및 허위 과대광고한 압소 14개소를 적발하였음

○ 이러한 제품중 비아그라 성분 및 유사성분에 함유된 제품은 의사의 처방없이 임의로 섭취하는 경우 국민건강을 크게 해칠 우려가 있음

○ 특히 일부제품은 1회 섭취 용량당 구연산실데나필이 최고 133.32mg까지 검출되거나, 용량계중 중에도 함유차이가 있는 등 균일하지 않아 섭취시 위험성이 있다고 밝혔다

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# Case #5 - Canada

Health Canada  
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April 5, 2002

2002-26  
April 5, 2002

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## Health Canada warns public not to use Hua Fo (DIN 02243366)

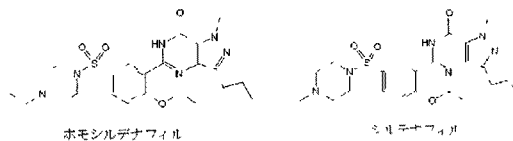
OTTAWA - Health Canada is warning consumers not to use Hua Fo tablets bearing the (Drug Identification Number) DIN 02243366, after they were found to contain an unauthorized substance similar, but not identical to, sildenafil. Sildenafil is a prescription drug approved for male erectile dysfunction, sold under the brand name Viagra®. Inappropriate use of sildenafil could cause severe adverse reactions.

### Similar, but not identical to, sildenafil

Health Canada issued a previous warning on February 15, 2002, concerning a lot of non-DIN Hua Fo that contained sildenafil. At the time, Health Canada required the importer to remove the product from the shelves. Health Canada is again requiring the importer and distributor to remove Hua Fo (DIN 02243366) from the market, and has issued a Customs Alert, to stop the importation of the product. Both the non-DIN and the DIN lots were sold in Canada by Shenlong Company Ltd.

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# Case #6 - Japan (2003. 12)



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# Case #7 - Korea

KFDA 식품의약품안전청

식품의약품안전청 > 식약청소개 > 식약청소개 > 보도/해명자료

2003.07.03

담당부서 식약관리과 작성일 2003.07.03  
 과장 오금현(吳均顯) 전화번호 380-1633  
 사무관 한일규(韓日圭) 전화번호 380-1515  
 제목 비아그라 주성분의 화학구조를 변형하여 식품으로 제조 판매한 업소 적발

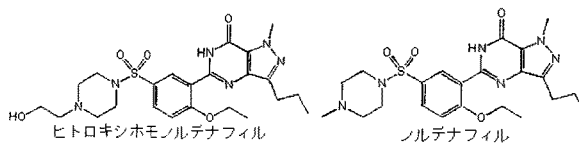
<주요내용>

- 식품의약품안전청은 건강의약품으로 허가된 알기부전 치료성분인 구연산염(비아그라 주성분)의 화학구조를 변형한 유사합성물질을 인삼제품에 넣어 남성기력식품으로 제조 판매한 8개 업소(제조업소 4개소 판매업소 4개소)를 적발하여 판매 시군구에 하여금 고발 행정처분을 조치하였다.
- 경기도 부천시 소재 "상원제약식품사업부"는 홍삼음료 "산타임 30ml×16 983병을 (주)상원모담 등에 제조 판매함
- 충남 부여군 소재 (주)퍼시픽트레이딩 은 홍삼음료 "갈락 및 하이-력 30ml×16 536병을 (주)상원바이오와 (주)Apex Global Co 등에 제조 판매함
- 강원도 속초시 소재 "해대린자생식품"은 인삼제품 "새오래 2g×18 780개 및 "새오래"분말 5g×5 5개를 (주)파울인그림"등에 제조 판매함
- 대구시 달서구 소재 신화제약식품사업부"는 인삼제품 "장력 300mg×138 720cap을 제조 판매함
- 식품의약품안전청은 글번에 적발된 "구연산염(비아그라)의 주성분)의 화학구조를 변형시킨 신종 합성물질에 대해 전문가 자문회의 결과 등 품질은 현행 동식물에서 존재하지 않는 화학적 합성물질임을 규명하고, 음질적으로 술(비아그라)로 증명하였다.

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# Case #8 - Japan (2004. 2)

[Redacted Box]



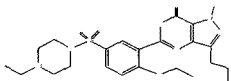
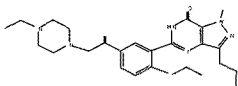
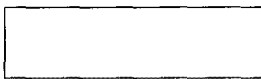
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## Banned-Viagra® and its Analogues in Food

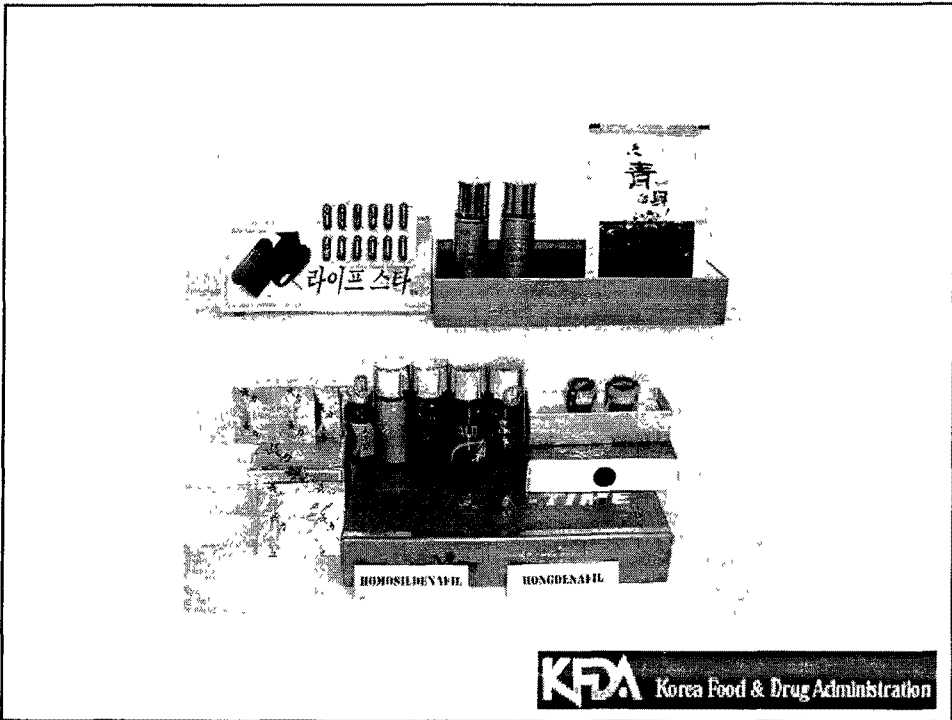
Compound Name	First Announced		Second Announced		Detected (mg/30mL)
	Country	Date	Country	Date	
Sildenafil citrate	Korea	July 2001	Canada	Feb. 2002	30-187
Tadalafil	Korea	Oct. 2002	USA	June 2003	20-60
Homosildenafil	Korea	April 2002	Japan	Dec. 2003	80-160
Hongdenafil	Korea	July 2003	-	-	25-132
Hydroxy homosildenafil	Japan	Feb. 2004	-	-	-

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## Illegal Foods Contained Sildenafil Analogues



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SAN-TIME

VP VP VP

TIME

남성의 힘! 바이탈 파워

왜 꼭 바이탈 파워?

남성의 힘! 바이탈 파워

왜 꼭 바이탈 파워?

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## Conclusion

- Sildenafil or Tadalafil were Detected in Imported Foods or Dietary Supplements
- New Analogues of Sildenafil were Identified in the Imported Chinese Herb Drinks, and their Chemical Structures Elucidated
- The Analogues were Named as 'Homosildenafil' and 'Hongdenafil', respectively
- Imported Foods Containing them have been Banned

