

Research: “ASSESSMENT OF THERAPEUTIC EFFECT  
OF SOFTGEL CRINUM LATIFOLIUM FOR BENIGN  
PROSTATIC HYPERTROPHY”

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## ABBREVIATIONS

Crinum latifolium	CL
Benign prostatic hypertrophy	BPH
Dihydrotestosterone	DHT
Luteinizing Hormone	LH
Luteinizing hormone-releasing hormone	LHRH
Sex Hormone Binding globulin	SHBG
Folliculine stimulator hormone	FSH
Lactate dehydrogenase	LDH
Fibroblastic growth factor	FGF
Basic fibroblast growth factor	bFGF
Transforming growth factor $\beta$	TGF $\beta$
International prostate symptom score	IPSS
Prostatic specific antigen	PSA
Total PSA	tPSA
Free PSA	fPSA
Tomodensitometry	TDM
Flutamid	FLU

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## **PART 1. INTRODUCTION**

Benign prostatic hypertrophy (BPH) - also known as benign prostatic hyperplasia, is one of diseases frequently seen in men above 45 years old. This condition attracts more and more consideration as the life-span is increasing, especially in developing countries, the prevalence of the disease is also gradually increasing with age and reaches 86% by the age of 81-90 years old. It is estimated that each year in US about 1.7 million of people have visits to hospital due to manifestations of this disease, among those 400.000 have surgical intervention. In Vietnam, according to an epidemiological survey conducted by Tran Duc Tho et al. in 3 regions North, Central, and South, it is shown that prevalence of the disease detected by ultrasonographic volume measurement ( $V_{gland} > 20\text{cm}^3$ ) is 63.8% in men above 50 years old, meanwhile it increases up to 73.1% in group  $\geq 75$  years old.

Actually the diagnosis of BPH is based on methods as follow:

- Clinical examination and assessment of urination problems
- Rectal examination
- Ultrasound examination of prostate
- PSA dosage

BPH causes urination problems which manifest by 2 main syndromes: irritative and obstructive, various complications such as infection, urinary retention, bladder stones, bladder diverticle, kidney failure... and influences patient's quality of life.

Currently there are different methods of treatment for urination problems secondary to BPH:

- + Medical treatment: hormonal products, Androgen antagonists, 5 alpha reductase inhibitors,  $\alpha 1$  adrenergic blockers, herbal remedies
- + Surgical treatment: prostate surgical removal, endoscopic prostate removal...

However in aged people there can be associated underlying conditions, thus surgical intervention can not be performed for all cases. Among medications some can cause side-effects, some are too costly.

*Crinum latifolium* is a kind of herb that is planted in various areas and used as herbal medication to inhibit the growth of tumor in uterus and prostate.

In order to develop the drug formulation for facilitating the usage and storage, National Phytopharma Joint-stock Company II has transformed dry glue of *Crinum latifolium* alkaloid to softgel.

We conduct the research “Assessment of therapeutic effect of softgel *Crinum Latifolium* for benign prostatic hypertrophy”. In this research the softgels of *Crinum Latifolium* manufactured by National Phytopharma Joint-Stock Company II are used to treat 189 patients suffering from BPH. The research is conducted at 3 centers:

- Vietnam National Institute of Gerontology – Bach Mai Hospital
- Hospital of Traditional Medicine, Ho Chi Minh City
- National Hospital of Traditional Medicine

Objectives of research:

1. To assess the therapeutic effect of softgel of *Crinum Latifolium* for benign prostatic hypertrophy after 2 months of using
2. To assess the side-effects of this drug after 2 month of using.

## **PART 2. OVERVIEW**

### **1. Some anatomical and physiological overview:**

Prostate and seminal vesicles are used as gateway to protect bladder and vas deferens, block or delay the attack of exogenous pathological factors. Prostate is an accessory sex gland which locates behind symphysis pubis, with uro-genital diaphragm from the top, in front of collecting rectum and vas deferens. Prostate consists of numerous zones and each zone has numerous glandular ducts which group in one opening into urethra.

The concept of prostatic division into lobes was not accepted recently. Since 1954, Frank believed that prostate is divided into different layers with one inner and one outer zone. Mc. Neal, Tissel and Solender 1975, Black lock, Resnick MI have shown the histological classification of prostate. The gland can be divided into 5 different zones:

1. The fibrous connective tissue in front is a thick layer which covers all anterior face of the gland. It consists of smooth muscles which envelop proximal urethra and penetrate into internal sphincter and detrusors. Fibrous connective tissue counts for 1/3 prostatic gland. There is no adenomatous structure in this zone. If this tissue is too developed it can squeeze the internal sphincter and detrusors and cause urination disturbances.

2. Peripheral zone: consists of several terminal tubules folded in front to form a small calyx around striate sphincter. This zone represents 70% of glandular tissue and often have cancer formation.

3. Central zone: includes all left part of gland which can be seen in this small central zone, it has contact with urethra at pubis. Histologically it is similar to seminal vesicles what makes people think that it has origin from Wolf tube. Like seminal vesicles, it can rarely transform to cancer.

4. Surrounding gland tissue: this is the smallest and most complicated zone which consists of both glandular and non-glandular tissue. It has cylinder smooth muscles and counts for about 1% of gland volume.

5. Transitional zone: contains a group of small tubules, which connect the distal and the proximal parts of urethra. It counts for about 5% of gland tissue and 15-30% of gland volume. Even though this zone is not big in quantity, not important in function but it is specific zone where benign prostatic hypertrophy develops.

Prostate is developed from uro-genital sinus, it starts development since 3<sup>rd</sup> gestational month of embryo, under action of DHT transformed from testosterone by 5-alpha deoxidase enzyme, 5-alpha deoxidase substance, which can only be seen in cells of uro-genital sinus, from week 12. Thus the differentiation of uro-genital sinus to form prostate. At the same time with formation of 5 alpha reductase enzyme in these cells, this is local action.

### ***Pathogenesis of benign prostatic hypertrophy***

Once prostate grows, it obstructs proximal part of urethra to cause the urethral diameter reduction, it is a mechanical obstruction. Prostate contains numerous fibers of smooth muscle, collagen and adenomatous tissue. The smooth muscle fibers in prostatic tissue and capsule and bladder neck are controlled by adrenergic and cholinergic systems especially alpha1 adrenergic. Once the ratio between smooth muscle fibers, collagen fibers and adenomatous tissue is changed, it leads to dynamic obstruction. Obstruction itself causes the instability of bladder contraction, resulting in hyperplasia, hypertrophy and collagen deposit in bladder. Thus it causes the loss of normal voiding reflex and reduces elasticity of bladder tissue. It is clear that there are numerous factors participating into pathogenesis of prostatic hyperplasia, but 2 predominant factors are testicles and age. As growth of prostate is regulated by androgen, during long period of time it was believed that prostatic hyperplasia is result of endocrine regulation. In the other hand there is undisputable evidence of role of stromal tissue in pathogenesis of prostate. All those things are to explain the prostatic overgrowth in aged people, including: role of hormones, impact of tissue interaction, between stromal and epithelial tissues, this is role of growth

factors, influence of inflammatory components, role of imbalance between cell proliferation and cell death due to decreased cell death in benign prostatic hypertrophy and prostatic cancer.

### *Hormones influencing the prostate growth*

#### *Testosterone*

This substance makes prostate grow. Hypothalamus of brain releases LHRH or GnRH, this substance stimulates pituitary gland to produce LH, LH binds to receptors on cellular membrane of testicles, synthesise and produce testosterone - the most potent androgen in the circulation. 95% of this substance is produced in testicles by Leydig cells. Testosterone concentration in venous blood is estimated at 40-50mcg/ml, thus 75 times higher than that in plasma, at about 600ng/ml plasma.

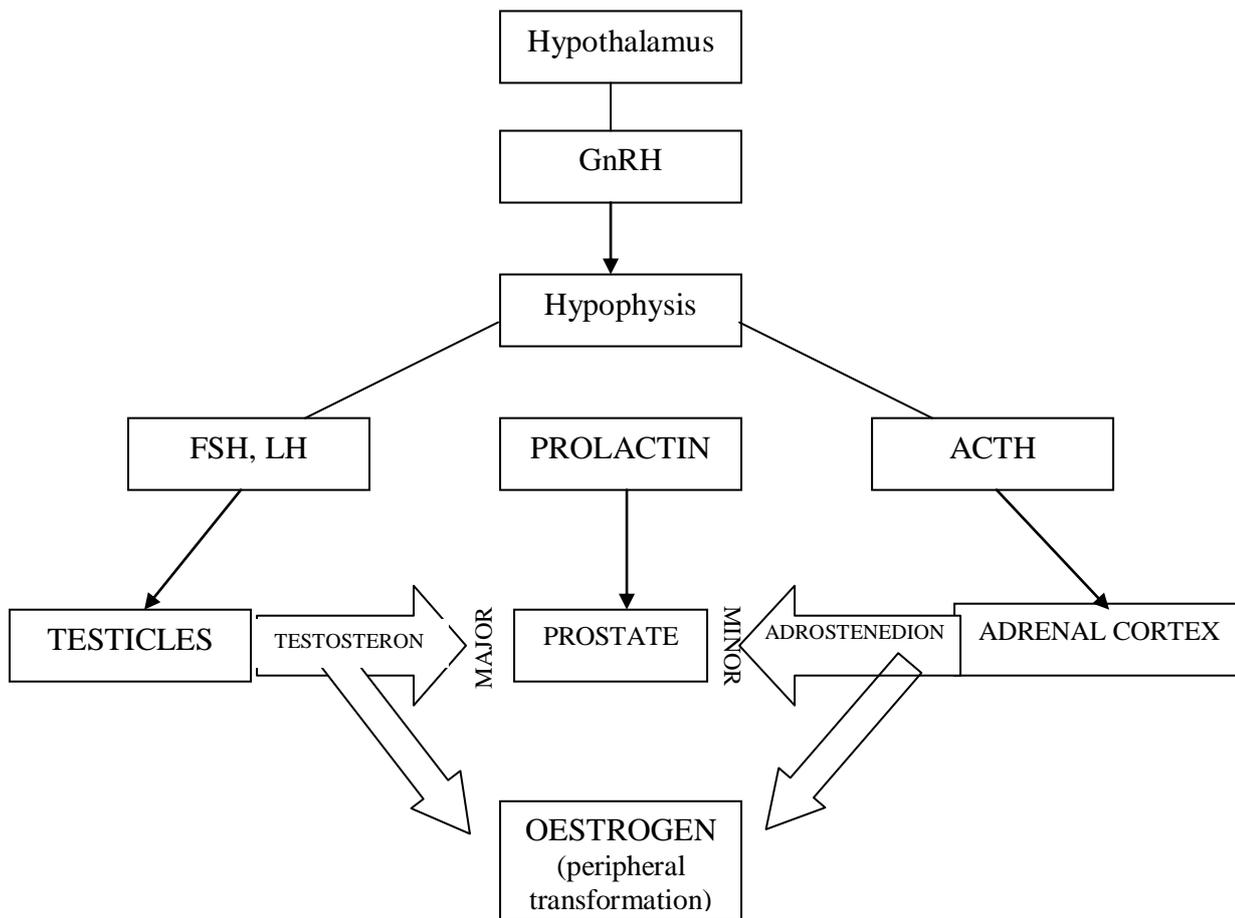
The real substance that causes prostate growth is DHT (Dihydro testosterone). This substance has 1.5-2 times stronger power than that of testosterone, but as it has too low concentration and is bind to protein so usually it has very little action. Its serum concentration is only equal to 10% of that of testosterone, at about  $56 \pm 26$ ng%. In opposite DHT originated from cells (prostate cells) is factor promoting prostate growth. Siteri and Wilson (1970) have first proved the increase of DHT in BPH at 3-4 times more than that in normal prostate.

This fact is confirmed by numerous other groups in the world Geller et al., Hammond 1978 (35), Neikle et al 1978, Kreig et al 1979, Lalph 1981.

DHT proportion in tissue is about 4-6ng/1g of hypertrophic prostatic tissue, meanwhile in normal case this proportion is 1-2ng/1g of tissue. Thanks to detection of receptors, nowadays people have consensus that proportion of androgen receptors is always increased in human hypertrophic or cancerous prostatic nodules.

#### *Role of estrogen*

In normal subjects estrogen has also role in controlling the prostate growth. This substance is metabolized in periphery from testosterone by enzyme aromatase.



Estrogen together with testosterone directly stimulate the prostate growth. At high dose, estrogen inhibits the prostate growth by blocking hypothalamus-hypophysis (negative feed-back) via hypophyseal LH system. One important estrogens component, which is the most potent, is estradiol, this substance has much higher concentration in prostate than in plasma.

Contrast to previous evaluation, estrogen does not inhibit the prostate growth but acts synergically with androgen. This action has been done experimentally on dogs by Walsh and Wilson and Klerk. The authors injected estradiol and DHT to castrated dogs and caused BPH. Furthermore people notice that estrogen increases proportion of androgen receptors and this results in synergic action of estrogen and androgen.

### *The adrenal androgens and prolactine*

The other factors that stimulate prostate growth are adrenal androgens and prolactine; there is no study over the last 30 years that could prove the direct action and key role of androgen for prostate growth which is observed in different investigations (Grayhack et all 1955, Danutra et all 1973). Prolactine also binds to prostate (Moger and Geschwind, 1972). Prolactine modifies the binding and metabolism of androgens too (Loyd et all 1973; Manand-Hanand-Har and Thomas 1976) and controls proportion of citric acid, fructose in

prostatic tissue. The prolactin receptors have been isolated from prostatic tissue (Argona, Freisen 1975).

### *LH and FSH*

LH is a hormone secreted from anterior pituitary; it stimulates Leydig cells in testicles to produce testosterone. In contrast circulatory testosterone has negative feedback action on hypothalamus-hypophysis axis.

### *Gonadotropin releasing factor*

Hypothalamus produces and secretes LHRH under the control of supra hypothalamic region. LHRH stimulates pituitary gland to produce LH and FSH both in human and in experiments. Its production happens by courses and under the control of central nervous system. This fact has been proved by experiments of Oesterling M.

### *Progesterone*

This is a hormone of corpus luteum in period of luteinization in women. Adrenal glands produce progesterone but only very small amount. The proportion which is secreted into blood is very low.

Even though elements of progesterone receptors which are differentiated in prostate have the corresponding concentration to that of androgen concentration, the substance can only be seen in cytosol (Ekman et al 1982) but never in cellular nucleus. Even its blood concentration is very low but the role of progesterone is remarkable as it has more affinity with 5 alpha reductase than testosterone does (Wright et al 1983) and many other progesterone-like effects such as cyproteron.

### *Growth factor*

There are 2 types of tissue in prostate: stromal (connective) and adenomatous (epithelial cells) tissue. These 2 types of tissue are controlled by androgen.

According to Mc Neal hypothesis (35) there are 2 periods of hyperplastic development of prostate: the first period is the formation of nodules consisting of pure connective tissue, and this interacted nodular period will form new epithelium. This hypothesis has been proved experimentally: while culture epithelial cells, they do not proliferate if there are no fibroblasts. Thus the regulation of prostatic epithelial development is mediated by stromal tissue.

The intermediate factors relevant to this issue are growth factors, which are polypeptides by chemical nature, and are synthesised and released by fibrotic plasmocytes (stromal cells), and epithelial cells. Growth factors impact cells through interaction, or mutual action. This results is regulated by interaction with specific protein or extra-membranous receptor. Numerous growth factors have been found in prostate, mainly are bFGF and TGF $\beta$ . Their main role in BPH has been elucidated by Lawson (36) and Cohen (37).

bFGF (Basic Fibroblast Growth Factor) is the key growth factor in human prostate development. bFGF is increased in prostatic hyperplasia. bFGF causes fibroblast mitosis and inhibits epithelial cell mitosis.

TGF $\beta$  (Transforming growth factor  $\beta$ ) down regulates fibroblast and epithelial cells growth.

During whole life, the microinjuries of urethral epithelium, of prostate surrounding urethra, during micturition, ejaculation or infection lead to release of bFGF from stromal tissue, epithelium and basal membrane. In its turn, bFGF creates the growth of stromal tissue with TGF $\beta$  modulation leading to prostatic hyperplasia.

In experiments, in culturing prostatic tissue it has been noticed that if there is enough testosterone but no growth factor in environment the cell growth won't happen. In adding to environment growth factor there will be cell growth. According to R. Lawson, the level of growth factor in patients with BPH is higher than in normal subjects and it is most concentrated in para-urethral area above verum montanum

## **II. Prostatic specific antigen (PSA).**

### *a) Origin and nature*

PSA has been found in 1971 in human semen. In 1979 Wang et all in Rosenwell Rark Memorial Academy first isolated PSA from human prostatic excretion. In 1980 serum PSA level could be measured and since 1988 PSA is widely used in clinical practice.

PSA is a glycopeptide with low molecular weight (34000) but high immune competency.

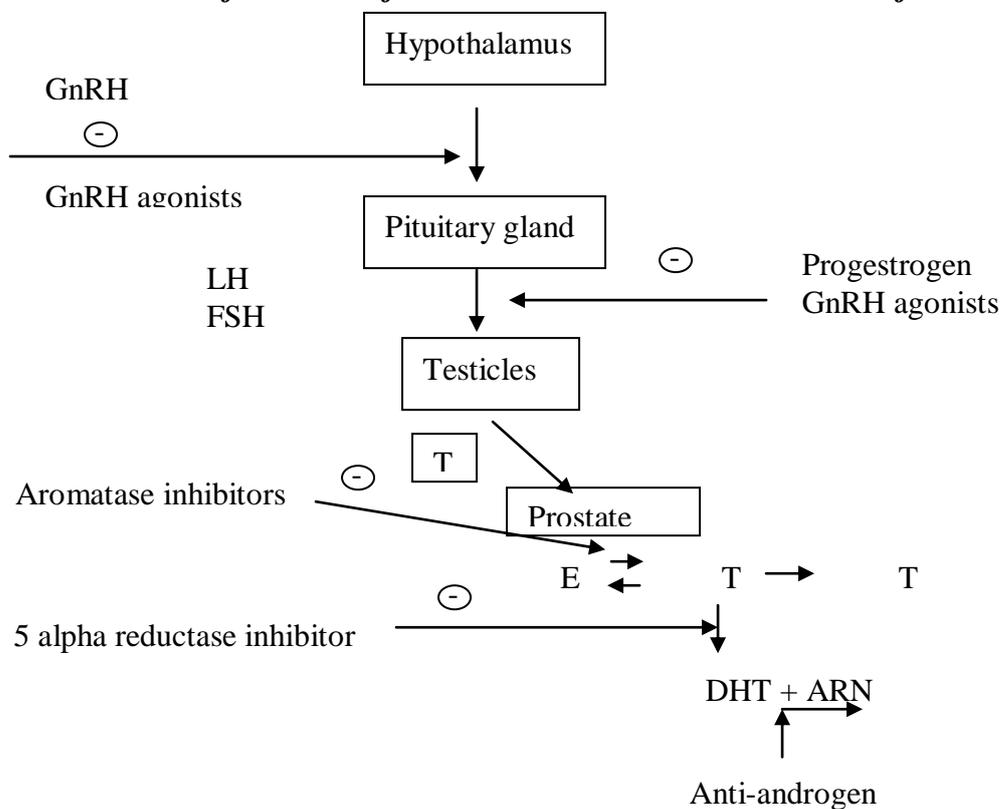
In normal condition PSA is responsible for liquidifying semen during ejaculation and modifying the small peptides in semen such as seminogene and fibronectine. PSA has potential inhibition action for vascular growth. The increase of serum PSA level in patients with prostate cancer is considered as reaction of body resistance against the malignization of gland epithelium.

*b) Normal level of serum PSA*

PSA is produced in adenomatous sinuses of prostate. At this site PSA concentration is a million times higher than that of serum. If the barrier that keeps PSA in adenomatous sinuses is destroyed, PSA is released into circulation via capillaries and lymphatic vessels resulting in raising of serum PSA level. In normal subjects, very small quantity of PSA has been excreted into serum, average half life of PSA is 2.5 days and it disappears completely after about 2 weeks.

In Vietnam, according to study led by Do Thi Khanh Hy PhD who combined the PSA dosage test with normal results of digital rectal examination, diagnosis of BPH is accepted at PSA level <10ng/ml.

***Schema: sites of actions of medications used in treatment of BPH***



**III. The published reports on treatment of BPH in the world**

Micturition problems secondary to BPH are very frequently seen condition in aged men. Even though the surgical treatment is effective but it cannot meet the needs because of the large number of patients. Furthermore, the aged patients usually suffer from various associated diseases thus many of them could and should have medical treatment.

Nowadays it is recognized that BPH is a condition secondary to excessive development of DHT, and caused by growth factors, from medical aspect, based on findings about pathogenesis of BPH, the medications that deprive androgen and growth factors have been found.

The trials on BPH treatment have been conducted using medications that could change the level in blood as well as in prostatic tissue and participate into process of androgen metabolism or inhibition of growth factors at target cells. Some of those treatment methods include the use in combination of anti-estrogen and anti-androgen, monotherapy by anti-androgen, use of growth factor inhibitors.

*The trials that are applied in clinical practice*

### **1. Finasteride**

Finasteride is a 5-alpha reductase inhibitor that was first used in urological practice for treatment of BPH, based on results of one recent observation: BPH is not found by digital rectal examination in patients with 5-alpha reductase deficiency. The two important trials that have been conducted in 1996 showed that Finasteride reduces significantly the risk of acute urinary retention and the rate of surgical interventions in patients with BPH (40). Recently a group from North America has reported the further reduction of prostatic volume, improvement of IPSS symptoms and of maximal urinary flow in patients with BPH treated by Finasteride more than 5 years (40). Group PROWSS has also showed that Finasteride improved clinical symptoms long-term and verified the reported above results (40).

### **2. Effect of alpha-adrenergic inhibitors in subjects with BPH**

More than 20 years ago, proportion of prescribed alpha-adrenergic inhibitors has rapidly been increased. These drugs have been used in clinical practice for treatment of lower urinary tract syndrome due to BPH in 1978; later the experiments have proved the predominance of adrenergic receptors in smooth sphincters in human prostate. At first phenoxybenzamine, one substance with long inhibition action on alpha 1, alpha 2 sympathetic receptor that Editorial and Gerstenberg have used for trial. Even it had positive effect on 2 aspects: urinary flow and urinary frequency in majority of patients, about 30% of cases manifested side-effects and one third of cases should discontinue treatment. Furthermore, phenoxybenzamine has oncogenic activity in rats as well as mutation action. Later on the alpha 1 sympathetic receptors have been discovered and they showed the selectivity of action, thus the drugs can be well tolerated and easier accepted, a large number of alpha 1 sympathetic drugs have come to clinical use: alfuzosine, doxazosine, indoramine, prazosine, terazosine. Next, one subtype of alpha 1 sympathetic receptors-alpha 1A, has been

discovered, thus another new drug which acts selectively on these receptors has been used: Tamsulosine. (40). The trials led by Hedllumd 1983, Kaczmarek 1992, Skirby using Prazosine as alpha 1 sympathetic inhibitor in a large group of patients, showed good results.

### **3. Effect of anti-androgen in subjects with BPH**

#### *Effect of progesterone*

Tran Duc Tho has used progesterone to treat 16 patients suffering from complete urinary retention due to BPH. At dose of 25mg, 2 ampoules a day, for 28 days (10 patients), and at dose of 5mg, 4 ampoules a day, for 50 days (6 patients).

The results showed that in 10 patients using 25mg, 2 ampoules a day, 3 patients passed some urine from day 3; 3 patients passed some urine from day 5; 4 patients passed some urine from day 7. All patients could urinate normally after 20 days of treatment and prostate volume has decreased after 1 month of treatment.

In 6 patients suffering from urination problems secondary to BPH and using the dose of 15mg, 2 ampoules a day, for 1 month (50 patients).

The results showed that after 1 month of treatment the symptoms of obstruction due to BPH have improved by 4 points in average, symptoms of irritation due to BPH have improved by 1.7 points. Prostate volume has decreased in all patients after 1 month of treatment.

Side-effects: 4 patients had discomfort sensation in 2 breasts, 1 patient had gynecomastia, 1 patient has decreased sexual activity. All side-effects have been resolved after treatment discontinuation.

In experiments, the study on progesterone effect showed that it had action to destroy the receptors on target cells (prostate cells).

### **The research works on herbal remedies**

#### *1. Effect of tadenan (pygeum africanum)*

##### *Origin:*

Tadenan is a drug which contains active substance extracted from skin of tree named *Pygeum africanum* (a kind of African plum), detected in 1970 by a French Pharmacologist. It has anti-inflammatory, anti-edematous effect in prostate, it increases the bladder elasticity, inhibits the growth of fibroblasts producing collagen, thus it can inhibit the development of BPH.

Dufour B. (48) has used tadenan to treat 60 patients with prostate tumor in France at dose of 25mg, 4 tablets a day, for 6 weeks.

The results showed the less frequency of urination during day time, the stronger urine flow, and the significantly less muscle contractions before to urinate.

In Vietnam the research work of Nguyen Thi Tuyet (7) has been conducted in 55 patients with BPH, among those 7 had urinary retention, those patients have used tadenan at 100mg/day for 6 weeks and had significant improvement of clinical symptoms, with IPSS score decreased from  $20.4 \pm 4.15$  to  $12.02 \pm 1.97$ , and the prostate volume has also decreased significantly.

### ***Crinum latifolium and conducted trials:***

*Crinum latifolium* tree is a herb belonging to Genus *Crinum* of 40-60cm in height, with bulb-form trunk similar to big onion, which has diameter of 10cm or more, leaves sprout around root and have linear form of 60-90cm in length, 5-11cm in width, with parallel veins and slightly waved margins, leaf blade is wide, leaves gather together to form a pseudotrunk, upper leaf face is pale purple. Bundle of flowers rises from one main pedicle and form a halo of 30-60cm in length, with 6-10 flowers of white - pale pink color nearly without pedicle, flower bud has lozenge form like a canarium fruit, the flowers in blossom have upper part of petals divided while lower part is closed, thus flower has form of funnel, with 6 stamen and 1 stigma.

Scientific name of herb is *Crinum Latifolium* L., it belongs to family Amaryllidaceae, with about 120 genera, which are distributed in tropical area. *Crinum* L. in Asia has 17 species, among those 3 are popular in Vietnam: *Crinum latifolium* L., *Crinum asiaticum* L., *Crinum ensifolium* Roxb. In addition 3 other species are *Crinum giganteum* Andr., *Crinum moorei* Hook.f. (origin from Africa) and *Crinum amabile* Donn.

In Chinese literature the herb is called “Thap bat hoc si”, “Tay nam van Chau Lan”

In the book of Vietnamese plants it is called “toi loi la rong”

According to Nguyen Cong Duc and Nguyen Thuong: leaf has hot taste, nature fresh, nearly non-toxic. Effects include: prevention of stasis of blood, anti-inflammatory, antalgic, disintoxication, circulation stimulation.

The tree grows commonly in China, India, Thailand, Cambodia, Vietnam. In Vietnam *Crinum latifolium* is grown it-self and is cultivated in Hue, Danang, Nha Trang and some Southern provinces, recently in some Northern areas.

Vietnamese people use fresh or dried leaves, some use trunk and bulb. In other countries the flowers, trunk and branches are used in dried slices (Do Tat Loi 2000).

In 1984 Ghosal (India) has purified and identified from flower petals of *Crinum latifolium* a glucoalkaloid named Latisolin. Under enzymatic hydroxylation an aglycol named latisodin has been purified. In 1986 Ghosal has reported the extraction of some alkaloids derivatives with anticancerous effect from *Crinum latifolium* - Crinafolin and Crinafolidin. In 1989 he has extracted from juice of *Crinum latifolium* flower petals 2 new alkaloids with pyrrolophenanthridin nucleus which are 2-epilycorin and 2-epipancrassidin.

According to Nguyen Binh (1998), the chemical composition of tree consists of: Glucans, organic acids, saponin, aminoacids, alkaloids.

- The glucans include glucan A and B.
- The aminoacids such as: phenylalanine, L-leucin, DL-valin, L-arginin monohydrochloride.
- The alkaloids are divided into 2 groups:
  - + Alkaloids without heterocyclic nucleus: latisolin, latisodin.
  - + Alkaloids with heterocyclic nucleus: Ambellin, 11-0-acetylbambellin, 11-0 acetyl 1,2- $\beta$  epoxyambellin, crinafolin, crinafolidin, lycorin, epilycorin, epipancrassidin, 9-0-demethylhomolycorin, lycorin-1,0-glucosid, pratorin (hippaddin), pratorinin, pratorimin, pratosin, beladin, latindin, latifin.

Since the years 1989-1990 the people in various areas of Vietnam use *Crinum latifolium* leaves for treatment of uterine fibromas, uterine cancer and BPH, prostatic cancer.

Basing on effects of *Crinum latifolium*, since 1991 Nguyen Thi Ngoc Tram et all. have conducted detailed studies on its characteristics and they have received very promising results. Alkaloid Lycorin is the main substance extracted from *crinum latifolium* L. which has stimulatory effect on T lymphocytes in vitro and in experimental rats, and reduces the viability of tumor cells. The infusion from *Crinum latifolium* can reduce tumor size in experimental rats.

September 2002 the acute toxicity of product has been verified by Nguyen Thi Ngoc Tram et all. in laboratory of Department of Traditional Medicine, School of Medicine and Pharmacy Ho Chi Minh City, and result showed: LD50 = 49.7g/kg body weight of rat. August 2003 semi-chronic toxicity has been verified in experimental traditional medicine lab at National Hospital of Traditional Medicine on 24 rabbits. The results did not show significant change of biochemical, hematological parameters in experimental groups at beginning and after 2 months of drug use.

Crinum latifolium bag has been used for treatment of BPH (Nguyen Xuan Huong, 2001). Treatment results: 97% have good response, gland volume decreased, urine flow increased, urination urgency decreased. Some patients had no signs of BPH on ultrasound examination.

In order to develop the drug formulation for facilitating the storage and usage, National Phytopharma Joint-Stock Company II produced softgel of Crinum latifolium. Softgel composition: 250mg dried extract corresponding 1.25mg whole alkaloid of Crinum latifolium.

*Some images of tree Crinum latifolium that we have used for study*

*Picture 1. Dried leaves of Crinum latifolium used for medication manufacturing*

*Picture 2. Whole tree, bulb and root of Crinum latifolium*

*Picture 3. Flower of Crinum latifolium*

### **PART III. MATERIAL AND METHOD OF STUDY**

#### **1. Material of study:**

Softgels made of dried extract which contains whole alkaloid of Crinum latifolium tree, manufactured by National Phytopharma Joint-Stock Company II at dosage of 1g/softgell.

*Picture 4. Product Softgel of Crinum latifolium manufactured by National Phytopharma Joint-Stock Company II*

#### **2. Subjects of study**

##### *2.1. Site of study:*

Divided into 3 major centers:

- National Institute of Gerontology (NIG) Bach Mai Hospital
- National Hospital of Traditional Medicine (NHoTM)
- Hospital of Traditional Medicine Ho Chi Minh City (HoTM HCMC)

##### *2.2. Number of patients:*

- At NIG: 60 patients
- At NHoTM: 66 patients
- At HoTM HCMC: 63 patients

Total: 189 patients

Each patient got treatment by softgel of Crinum latifolium: 8 gels/day in 2 divided doses administered 1 hr after meal. Duration of using: continuously for 60 days (2 months).

##### *2.3. Criteria of inclusion:*

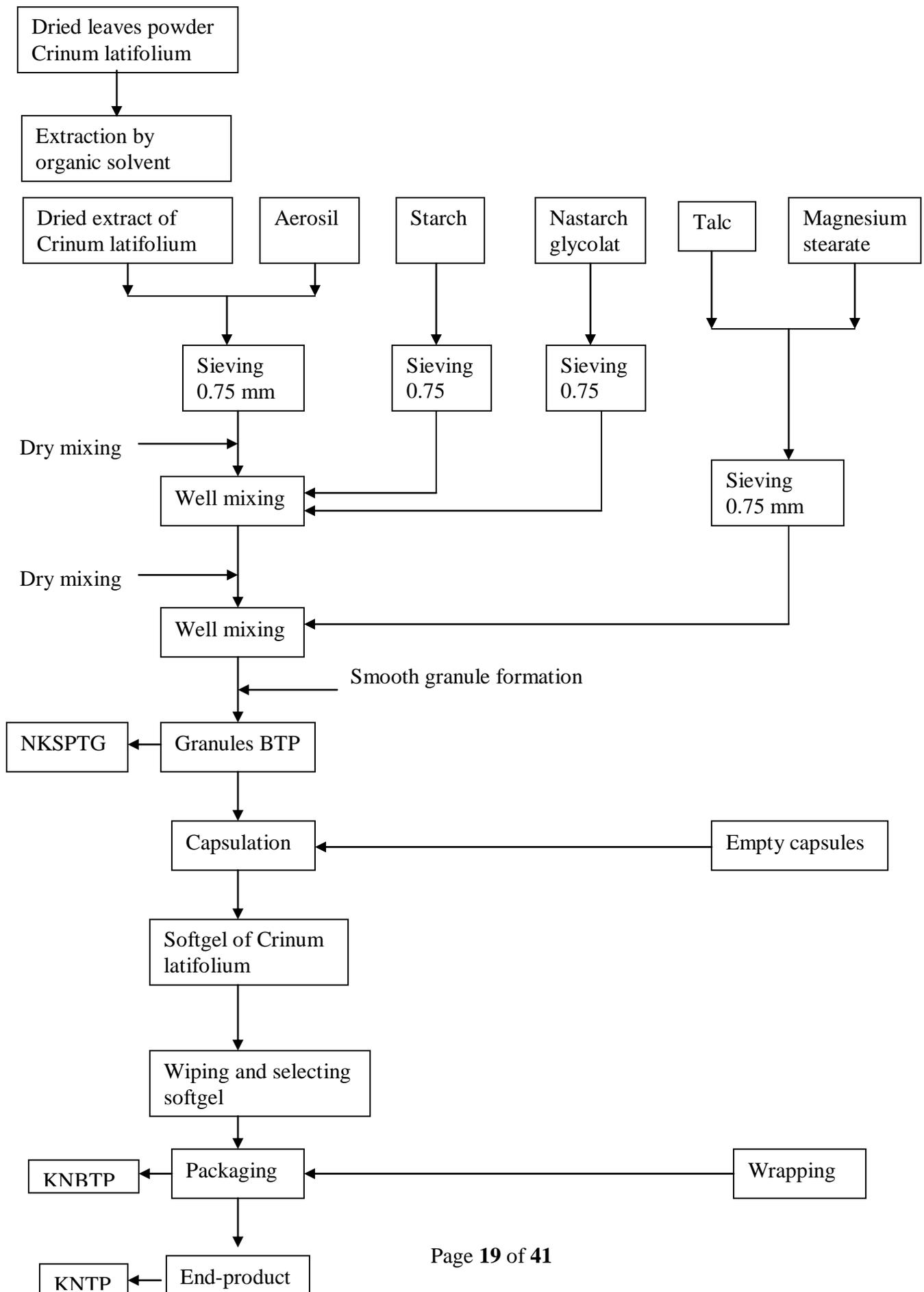
The patients over 50 years old voluntarily come to visits and have confirmative diagnosis of BPH

- + Patients have urination problems from moderate to severe degree with IPSS  $\geq 8$
- + Ultrasound examination reveals volume of gland  $>20\text{gr}$
- + Digital rectal examination reveals enlarged prostate, smooth surface, well defined borders, not painful in palpation
- + Biology: serum creatinine normal, SGOT, SGPT normal
- + Test of PSA  $< 10\text{ng/ml}$ .

*2.4. Criteria of exclusion:*

- + Suspected cancer
- + PSA  $> 10\text{ng/ml}$
- + Complete urinary retention
- + Urinary tract diseases: kidney failure, kidney stones, UTI
- + Patients refuse to voluntarily participate into study
- + Patients do not use medication as required in study protocol, do not come for revisits after treatment course.

### The manufacturing steps



## 2. Method of study:

Open-labeled, interventional, observational, uncontrolled trial, follow-up and evaluation of results collected from some in-patients and out-patients.

For all patients medical history has been taken, clinical and digital rectal examination, biological tests have been performed:

- + Electrocardiography
- + Full blood count
- + Urea, creatinin
- + Blood sugar
- + Liver enzymes: SGOT, SGPT
- + PSA
- + Urinalysis
- + Ultrasound examination of urinary tract, prostate, measure of residual urine volume

Data analysis using statistical program SPSS for window 10.0, Student's T-test for a series of value couples before and after study.

### *a. Tools of study*

- Open-labeled clinical trial, comparing results before and after drug using. The followed parameters:
- Assessment of severity of urination symptoms using IPSS score scale and Quality of Life Score Scale:

### SCORE BOARD FOR ASSESSING SYMPTOMS OF BENIGN PROSTATIC HYPERTROPHY BASING ON INTERNATIONAL SCORE SCALE (IPSS)

Patient name: ..... Age: .....

Urinary symptoms over the past month	Circle the score corresponding to question					
	Not at all	≤ 1/5 times	≤ 1/2 times	= 1/2 times	≥ 1/2 times	Always
<b>1. Incomplete emptying bladder:</b> Did you have the sensation of having urine in bladder after you finished urinating?	0	1	2	3	4	5
<b>2. Frequent urination:</b> Did you have to urinate again within 2 hrs?	0	1	2	3	4	5
<b>3. Hesitancy in urinating:</b> Did you often have to stop abruptly during urination and start again?	0	1	2	3	4	5
<b>4. Urgency of urination:</b>	0	1	2	3	4	5

Did you have difficulty to postpone urination?						
<b>5. Weak urinary stream:</b> Did you notice the weak urinary stream?	0	1	2	3	4	5
<b>6. Effort in urinating:</b> Did you have to push when starting urination?	0	1	2	3	4	5
<b>7. Norturia:</b> How many times did you have to get up to urinate at night?	0	1 time	2 times	3 times	4 times	5 times

**Total score: .....**

Maximum score for 5 questions is 35

- + Mild symptoms: 0-7 points
- + Moderate symptoms: 8-19 points
- + Severe symptoms: 20-35 points

#### CALCULATING SCORE FOR QUALITY OF LIFE

	How would you feel if you had to spend the rest of your life with urinary problems as they are now?						
	Delighted	Pleased	Satisfied	Passable	Little uncomfortable	Unhappy	Intolerable
Score	0	1	2	3	4	5	6

#### **Total score 0-6 points**

- + Mild: 0-2 points
- + Moderate: 3-4 points
- + Severe: 5-6 points

#### *b. Digital rectal examination:*

For all patients digital rectal examination has been done before and after treatment course.

Patients are in supine position, legs flexed, form an angle 60-70° between thigh and horizontal surface, 2 thighs are abducted. Doctor stays at patient's right side, with left hand placed on patient's pubis symphysis, insert index of gloved and lubricated by paraphine right hand into patient's rectum. Patient breaths regularly, relax abdomen. Through digital rectal examination one could assess:

- Prostatic consistency: firm, soft or very hard
- Prostatic surface: smooth or rough, with nodules or not
- Sensibility: painful or not in palpating

*c. Method of measuring gland volume and mass*

We used ultrasound machine Siemens Sonoline-Versa-Pro with real-time linear electronic probe 3.5MHz to conduct exploration of patients' prostate. Measure prostate volume by transabdominal suprapubic ultrasound examination, patient is in supine position with full bladder.

Ultrasonographic assessment of: density, homogeneity, morphological changes, gland size, associated lesions.

Calculate gland volume by Ellisoide using formula:

$$V = H.L.E \times 0.523$$

Or using formula:

$$V = \frac{H.L.E}{2}$$

Where: H: gland height  
L: gland width  
E: gland depth

Consider volume in cm<sup>3</sup> of tissue approximately equal to 1gr.

If prostate volume measured by ultrasound examination is >20cm<sup>3</sup>, it is considered BPH.

Next, after patients empty their bladders, measure residual urine volume. Conduct ultrasonographic measurement of prostate volume and residual urine volume at 3 moments:

- + At first visit
- + After 1 month of treatment
- + After 2 months of treatment

Test SGOT, SGPT, serum creatinin, full blood count, urinalysis before and after drug use. Compare the results obtained before and after drug use.

*\* Assessment of results after treatment.*

- Good results:

- + Prostate size normalizes after 2 months of treatment
- + Score of IPSS and of Quality of Life (QOL) is rated as mild

- Fair results:

- + Prostate size reduces in comparison with baseline
- + Score of IPSS and of QOL changes significantly.

- Poor results:

- + Prostate size remains unchanged or even increases after treatment
- + Score of IPSS and of QOL changes non-significantly

\*Assessment of drug adverse effects:

- + Note the occurrence of allergic reactions, itchy rash, urticaria.
- + Liver function: SGOT, SGPT
- + Kidney function: serum creatinin, urea, proteinuria, hematuria, leucocyturia
- + Full blood count, urinalysis

Ethic of investigation:

This softgel is originated from a herb which has been used in population since longtime.

The study is aimed to improve the treatment effect for patients, not to cause any harm for patients.

Patients participating into study are voluntary and they seek Crinum latifolium softgels for treatment.

## **PART IV. STUDY RESULTS**

### **I. STUDY RESULTS ON CLINICAL CHARACTERISTICS**

#### **1. The number of patients**

- At NIG: 55 patients enrolled from total 60 recruited (5 dropped out as they did not come for revisits)

- At HoTM HCMC: 50 patients enrolled from total 63 recruited (13 dropped out)

- At NHoTM: 52 patients enrolled from total 66 recruited (14 dropped out as their PSA >10ng/ml and they did not comply with the treatment protocol)

-Total number of patients enrolled in 3 centers: 157.

#### **2. Age group**

*Table 1: Patient distribution by age groups*

<b>Age, years</b>	<b>Number of patients (n)</b>	<b>Proportion (%)</b>
50-59	13	8.28
60-69	67	42.68
70 and +	77	49.04
<b>Total</b>	<b>157</b>	<b>100</b>

- The youngest is 50 years old, the oldest is 87 years old
- Majority of patients belong to age group of  $\geq 60$  years: 144 people (91.72%)

### 3. Duration of being affected

*Table 2: Duration from onset of disease*

<b>Duration from onset</b>	<b>Number of patients (n)</b>	<b>Proportion (%)</b>
< 1 year	19	12.1
1-5 years	100	63.7
6-10 years	28	17.8
> 10 years	10	6.4
<b>Total</b>	<b>157</b>	<b>100</b>

Table 2 shows that the duration from onset is usually 1-5 years (76%).

### 4. Digital rectal examination

The patients have passed digital rectal examination: before treatment, at revisit time: after 1 month, after 2 months.

*Table 3: Prostate consistency before and after treatment  
At National Institute of Gerontology*

<b>Prostate consistency</b>	<b>Before treatment</b>		<b>After 1 month</b>		<b>After 2 month</b>	
	n	%	n	%	n	%
<b>Firm</b>	70	65.4	41	38.3	34	31.8
<b>Soft</b>	37	34.6	66	61.7	73	68.2
<b>Total</b>	<b>107</b>	<b>100</b>	<b>107</b>	<b>100</b>	<b>107</b>	<b>100</b>

### 5. Dosage of serum PSA

*Table 4: Average of PSA level*

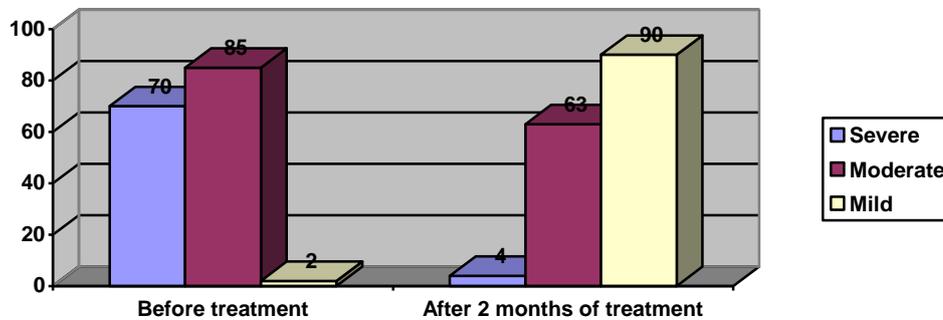
<b>Average PSA level by age group</b>	<b>National Institute of Gerontology</b>		<b>National Hospital of Traditional Medicine</b>	
	<b>Number (n)</b>	<b>PSA ng/ml <math>\bar{X} \pm SD</math></b>	<b>Number (n)</b>	<b>PSA ng/ml <math>\bar{X} \pm SD</math></b>
50-59 years old	7	3.87 $\pm$ 2.49	2	3.60 $\pm$ 0.56
60-69 years old	18	2.99 $\pm$ 2.14	24	3.82 $\pm$ 2.10
70 and + years old	30	3.39 $\pm$ 2.28	26	4.84 $\pm$ 2.59
<b>Total</b>	<b>55</b>	<b>3.322 <math>\pm</math> 2.24</b>	<b>52</b>	<b>4.32 <math>\pm</math> 2.33</b>

Average PSA level at 2 centers: NIG and NHoTM is 3.80  $\pm$  2.283ng/ml.

## II. TREATMENT RESULTS

### 1. Assessment of severity degree using IPSS symptomatic scoring system at 3 centers

*Graph 1: Severity of urination symptoms by IPSS scoring system*



Graph 1 shows that number of patients suffering from severe urination symptoms after treatment decreases significantly, number of patients suffering from moderate and mild urinary symptoms increases significantly.

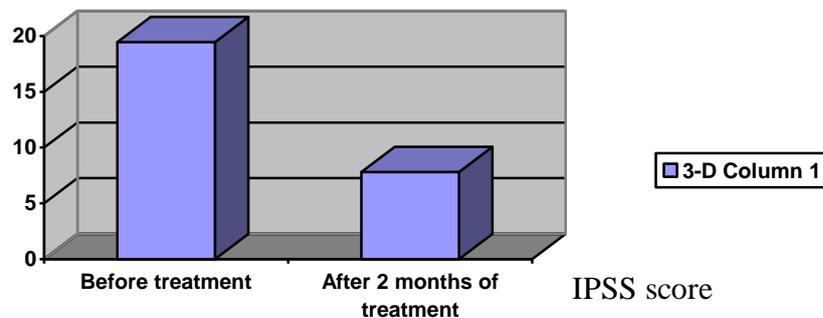
### 3. Result of total average IPSS score before and after treatment

*Table 5. Average IPSS symptomatic score before and after treatment*

Average IPSS	Before treatment $\bar{X} \pm SD$	After 2 months $\bar{X} \pm SD$	Number of patients (n)	p
NIG	$19.8 \pm 5.36$	$8.29 \pm 5.17$	55	<0.001
HoTM HCMC	$17.12 \pm 4.79$	$11.8 \pm 3.88$	50	<0.001
NHoTM	$21.32 \pm 5.5$	$3.48 \pm 2.00$	52	<0.001
<b>Total</b>	<b><math>19.45 \pm 5.22</math></b>	<b><math>7.81 \pm 3.71</math></b>	<b>157</b>	<b>&lt;0.001</b>

- Table 5 shows that after treatment there is a significant improvement of systematic score.

*Graph 2. Systematic IPSS score before and after 2 months of treatment*



#### 4. Result of quality of life score

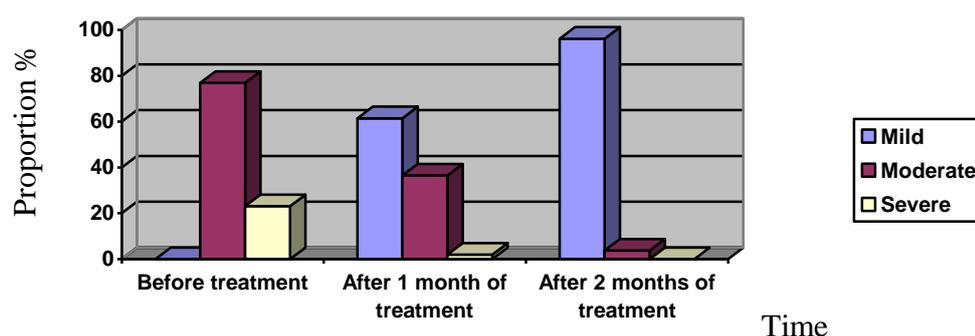
QOL score assesses the patients' satisfaction towards the urinary symptoms, the patients' adaptation to symptoms, it corresponds to symptomatic IPSS score

*Table 6: Quality of life score before and after treatment  
At NIG and HoTM HCMC*

QOL score	Before treatment $\bar{X} \pm SD$	After 2 months $\bar{X} \pm SD$	Number of patients (n)	p
NIG	3.74 $\pm$ 0.65	2.65 $\pm$ 0.73	55	< 0.001
HoTM HCMC	3.32 $\pm$ 0.65	2.82 $\pm$ 0.43	50	< 0.001
<b>Total</b>	<b>3.54 <math>\pm</math> 0.65</b>	<b>2.73 <math>\pm</math> 0.58</b>	<b>105</b>	<b>&lt; 0.001</b>

Table 6 shows that results of QOL average score at NIG and HoTM HCMC improve significantly after treatment from 3.54 to 2.73.

*Graph 3: Assessment of severity of urinary symptoms before and after treatment using QOL score scale at NhoTM*



Results shown on graph 3: QOL score at NhoTM shows that after 1 month of treatment patients obtain mild improvement of AOL from 0% before treatment to 61.5% and further to 95.2% after 2 months of treatment. In contrast, the proportion of patients rating severe degree of QOL score decreases from 23.1% to 1.9% after 1 month and 0% after 2 months of treatment. The number of those who have score at moderate degree also decreases significantly from 76.9% to 36.5% after 1 month and to 3.8% after 2 months of treatment.

#### 4. Results of parameters pulse, blood pressure

*Table 7: Heart rate*

Heart rate	Before treatment $\bar{X} \pm SD$	After treatment $\bar{X} \pm SD$	Number of patients (n)	p
NIG	83.27% $\pm$ 10.57	83.04 $\pm$ 7.92	55	> 0.05
HoTM HCMC	82.20 $\pm$ 6.62	82.32 $\pm$ 5.445	50	> 0.05
NhoTM	78.0 $\pm$ 6.8	78.0 $\pm$ 5.2	52	> 0.05
<b>All 3 centers</b>	<b>81.18 <math>\pm</math> 8.06</b>	<b>81.14 <math>\pm</math> 6.23</b>	<b>157</b>	<b>&gt; 0.05</b>

Table 8: Blood pressure

BP (mmHg)		Before treatment X ± SD	After treatment X ± SD	Number of patients (n)	p
NIG	SBP	136.73 ± 20.29	131.73 ± 11.04	55	> 0.05
	DBP	81.53 ± 13.02	80.46 ± 10.27		
HoTM HCMC	SBP	130.8 ± 10.65	132.40 ± 9.38	50	> 0.05
	DBP	81.9 ± 5.03	81.3 ± 5.95		
NhoTM	SBP	128.13 ± 11.88	124.23 ± 8.98	52	< 0.05
	DBP	80.19 ± 7.79	76.63 ± 6.31		
All 3 centers	SBP	<b>131.99 ± 14.43</b>	<b>129.46 ± 9.93</b>	<b>157</b>	<b>&gt; 0.05</b>
	DBP	<b>81.2 ± 8.81</b>	<b>79.45 ± 7.58</b>		

### 5. Results of measuring the prostate volume before and after treatment:

Table 9: Results of measuring prostate volume before and after treatment

Prostate volume (cm <sup>3</sup> )	Before treatment X ± SD	After 2 months of treatment X ± SD	Number of patients (n)	p
NIG	39.87 ± 14.60	35.00 ± 13.82	55	< 0.05
HoTM HCMC	38.07 ± 13.72	33.94 ± 12.19	50	< 0.05
NhoTM	38.88 ± 14.61	36.20 ± 18.99	52	< 0.05
<b>All 3 centers</b>	<b>38.97 ± 14.32</b>	<b>35.06 ± 15.01</b>	<b>157</b>	<b>&lt; 0.05</b>

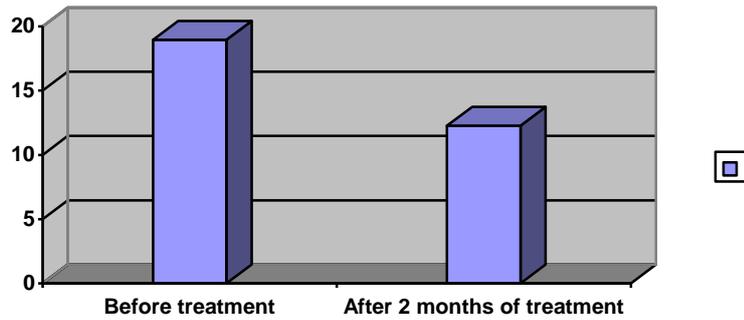
Table 9 shows that after 2 months of treatment average prostate volume non-significantly decreases.

### 6. Volume of residual urine

Table 10. Volume of residual urine before and after treatment

Volume of residual urine (cm <sup>3</sup> )	Before treatment X ± SD	After 2 months of treatment X ± SD	Number of patients (n)	p
NIG	24.25 ± 26.72	17.30 ± 16.53	55	<0.05
HoTM HCMC	20.47 ± 24.17	15.03 ± 13.64	50	<0.05
NhoTM	11.86 ± 14.61	4.30 ± 9.57	52	<0.05
<b>All 3 centers</b>	<b>18.94 ± 21.89</b>	<b>12.27 ± 13.30</b>	<b>157</b>	<b>&lt;0.05</b>

Table 10 shows that after 2 months of treatment the volume of residual urine decreases.



Graph 4. Volume of residual urine before and after 2 months of treatment

## 7. Results of biochemical, hematological and urine analysis findings before and after treatment:

### a. Biochemical tests

Table 11: Biochemical findings, liver enzymes

	Before treatment <b>X ± SD</b>	After 2 months of treatment <b>X ± SD</b>
Urea (mmol/l)	6.07 ± 1.76	5.86 ± 1.39
Creatinin (µmol/l)	102.14 ± 14.52	100.02 ± 14.45
SGOT (UI/l)	29.03 ± 9.38	30.43 ± 10.47
SGPT (UI/l)	27.08 ± 15.58	26.83 ± 12.33
<b>n</b>	<b>157</b>	
<b>p</b>	<b>&gt;0.05</b>	

The results show that liver function, kidney function expressed by liver enzymes values, urea, creatinin non-significantly change with  $p > 0.05$

### b. Full blood count

Table 12: Results of full blood count

	Before treatment <b>X ± SD</b>	After treatment <b>X ± SD</b>	<b>n</b>	<b>p</b>
White blood count (thousand/ml)	6.35 ± 1.145	6.58 ± 0.934	<b>157</b>	<b>&gt;0.05</b>
Red blood count (million/ml)	4.418 ± 0.422	4.59 ± 0.376	<b>157</b>	<b>&lt; 0.05</b>

Results of FBC show:

- WBC does not change significantly with  $p > 0.05$
- RBC increases slightly but remains within normal ranges ( $p < 0.05$ )

### c. Results of urinalysis:

55 patients have urinalysis at NIG and results show:

*Table 13: Results of urinalysis at NIG*

<b>At NIG</b>	<b>Before treatment X ± SD</b>	<b>After treatment X ± SD</b>	<b>Number of patients (n)</b>	<b>p</b>
Urinary pH	5.8914 ± 0.750	6.0629 ± 0.7841	55	>0.2
Urinary specific density	1018.89 ± 7.5	1016.85 ± 7.73	55	>0.1

- There were 5 patients who had proteinuria less than 0.3g/l. After 2 months of treatment the amount of proteinuria of them changed significantly. All those 5 have hypertension.

- 3 patients have hematuria and leucocyturia, but amount is not important
- The urinalysis results of 52 patients at NhoTM show:

*Table 14: The parameters of urinalysis at NHoTM*

Time Parameters	Before treatment	After treatment	p
GLU (neg)	52/52	51/52	> 0.05
BIL (neg)	52/52	52/52	
KET (neg)	48/52	49/52	
SG (norm)	52/52	52/52	
pH (norm)	52/52	52/52	
PRO (neg)	52/52	52/52	
URO (neg)	52/52	51/52	
BLO (neg)	48/52	50/52	
LEU (neg)	51/52	52/52	

## 8. Composite results during treatment course

*Table 15: Composite results after 2 months of treatment*

Composite result	NIG		HoTM HCMC		NHoTM		All 3 centers	
	n	%	n	%	n	%	n	%
<b>Good</b>	21	38.18	9	18	40	79.6	70	44.59
<b>Fair</b>	20	36.36	40	80	10	19.2	70	44.59
<b>Poor</b>	14	25.46	1	2	2	3.9	17	10.82
<b>Total</b>	<b>55</b>	<b>100</b>	<b>50</b>	<b>100</b>	<b>52</b>	<b>100</b>	<b>157</b>	<b>100</b>

- Good results mean patients recognize marked improvement of urinary symptoms after treatment, IPSS score remains within mild degree less than 8 points, QOL score decreases markedly, patients feel comfortable, prostate volume and volume of residual urine also decrease.

- Good result: seen in 70 patients (44.59%)

- Fair result: seen in 70 patients (44.59%), patients have improved symptoms, QOL, volume of residual urine, but prostate volume decreases moderately,

- Poor result: seen in 17 patients (10.82%), no significant improvement of symptoms and of prostate volume.

## 9. Drug side effects:

*Table 16: Drug side effects*

	NIG (n)	HoTM HCMC (n)	NHoTM (n)	All	
				n	%
Dizziness	4	0	0	0	0
Insomnia	1	0	0	1	0
Allergy (suspicion)	1	1	0	2	1.27
Other	5	0	12	17	10.82
<b>Total</b>	<b>11</b>	<b>1</b>	<b>12</b>	<b>20</b>	<b>12.73</b>

- 2 patients (1 from NIG, 1 from HoTM HCMC) manifested urticaria, itchy rash after administration of drug, among them one takes simultaneously Nifedipine for hypertension, after stop using Nifedipine and take a 5-day course of anti-histaminic agent the symptoms resolved, patient continues taking drug and does not have further allergic manifestations. One patient at HoTM HCMC has history of bronchial asthma, the itchy rash resolved itself after 1 day, this patient continues treatment without noticing any event.

- 17 patients had mild symptoms of GI upset (such as mild abdominal distension, nausea, drug odor regurgitation, thirst) during the first days of drug using, a week later these symptoms have settled, only one patient with history of gastritis still notices mild abdominal distension.

- One patient suffers from insomnia after using drug during 1 week.

- 5 patients noticed mild dizziness after drug has been taken, they adjusted by having breakfast with more quantity thus symptoms reduced and disappeared, patient can live normal life and no one has to give up drug administration.

In brief, the drug side effects are mild, not too uncomfortable for majority of patients.

## **PART 5. DISCUSSION**

### **1. Discussion about some clinical characteristics of studied patients:**

Number of patients who voluntarily participated into study at 3 centers was 189, among those 32 have been dropped out because they did not come for revisits, did not comply with treatment protocol, and blood PSA>10ng/ml.

- At NIG 60 patients recruited, 5 of them have been dropped out as they did not come for revisits.

- At HoTM HCMC 63 patients recruited, 13 of them have been dropped out as they did not comply with treatment protocol

- At NHoTM 66 patients recruited, 14 of them have been dropped out as they had high blood PSA or did not comply with treatment protocol.

In total 157 patients completed the study, including in-patients and out-patients.

#### *1.1 Age:*

- Age from 50-86 years old  
- Average age is 69.45 years old  
- Majority of patients belong to age group >60 years old (144 patients) which count for 91.72%. The group of age from 60-69 years old: 67 patients, group of > 70 years old: 70 patients, among those 11 patients >80 years old.

#### *1.2. Time of onset*

Basing on medical history, onset of urinary symptoms, and 3 patients who have BPH detected by ultrasound during previous visits at the other hospitals, we found the time of onset of all patients is from 2 months to 15 years.

Most of patients have symptoms during 1-5 years (100 patients, corresponding 63.7%).

56 patients have been treated by traditional medicines or other medications earlier. They stopped using these medications more than 3 months prior to our first visit. The medications that have been frequently used are: alpha-blockers (carduran, xatral), tadenan, self-made extract from leaves of *crinum latifolium*.

### *1.3. Digital rectal examination:*

We conducted digital rectal examination at the first visit, after 1 month of treatment, and after 2 months of treatment.

In 107 patients at 2 centers (NIG and NHoTM) we noticed the softening of gland consistency after treatment: before treatment 70/107 patients had firm consistency of gland by digital rectal examination, this number was 34/107 after treatment.

The softening of gland consistency could explain the improvement of urinary symptoms better than the reduction of gland volume.

Even though the findings of digital rectal examination are very difficult to be quantified as the examination is subjective and examiner-dependent, but it is an essential clinical procedure for all practitioners.

## **2. Discussion about the effects of *Crinum latifolium* softgels on patients with urinary symptoms due to BPH**

### *2.1. The onset of effect and the maximal peak of effect*

- In 140/157 patients in this study started noticing the effect of medication after 2 weeks of taking it, the maximal effect has been reached after 8 weeks of treatment.

- Urinary symptoms have been improved for both irritative and obstructive.

### *2.2. For irritative symptoms:*

- Nouria is one of the symptoms that causes most discomfort to patients as they have to wake up at night for urinating and thus they cannot sleep.

- In 55 patients participating into study at NIG: before treatment patients had to wake up in average  $2.53 \pm 1.35$  times/night, after 2 months of treatment this number has reduced to  $1.27 \pm 1.78$  times/night, difference is significant with  $p < 0.005$ . Urination urgency average score before treatment was  $1.67 \pm 1.93$ , which reduced to  $0.67 \pm 1.44$  after treatment significantly with  $p < 0.005$ .

- In 52 patients participating into study at NHoTM: after treatment completed the number of patients who needed to wake up at night for frequent urination reduced:

+ Before treatment 29 patients had to wake up 2-3 times/night for having urination, this number was 12 after treatment.

+ Before treatment 17 patients had to urinate more than 4 times/night, after treatment there was no one who should urinate more than 4 times/night.

### 2.3. *For obstructive symptoms:*

- For 55 patients at NIG we notice:

Incomplete urination has also been reduced significantly, from average score of  $4.0 \pm 1.79$  before treatment to  $1.49 \pm 1.91$  with  $p < 0.005$

Interrupted urination has reduced significantly average score from  $3.08 \pm 1.82$  before treatment to  $1.25 \pm 1.64$  after treatment with  $p < 0.005$ .

Weak urination had average score before treatment  $4.02 \pm 1.66$  which has been significantly reduced to  $1.39 \pm 1.97$  with  $p < 0.005$

Urination with efforts has also been improved, the average score  $1.63 \pm 1.99$  before treatment has significantly reduced to  $0.69 \pm 1.16$  with  $p < 0.005$ .

### 2.4. *The composite symptomatic score IPSS*

- Symptomatic score scale IPSS is a scale to quantify the urination symptoms.

In 157 patients participating into study at 3 centers (graph 1 and table 5) we noticed that:

- Before treatment 70 patients (44.59%) had urination symptoms at severe degree, IPSS more than 20 points, 85 patients (54.14%) - moderate degree, and 2 patients (1.27%) - mild degree. After 2 months of treatment the number of patients with severe symptoms reduced significantly to 4 (2.55%), the number of patients with moderate symptoms reduced to 63 (40.13%), and the number of patients with mild symptoms increased significantly to 90 (57.32%).

- Average score IPSS reduced significantly from  $19.45 \pm 5.22$  before treatment to  $7.81 \pm 3.71$  after 2 months of treatment ( $p < 0.001$ )

Thus after 2 months of treatment the number of patients who presented with severe symptoms has significantly reduced, also as the average score of IPSS. Comparing with other study on herbal remedies (Tadenan) published by Nguyen Thi Tuyet (7) the degree of improvement of symptomatic score scale was similar (from 20 to 12.02 after 6 weeks of using Tadenan).

### 2.5. *Quality of life score:*

- The QOL score assesses the satisfaction of patients regarding the urinary symptoms, the adaptation of each patient to these symptoms, and it is corresponding to IPSS scoring scale. This score is divided to 3 degrees (from 0 to 6 points):

- + Mild degree: from 0-2 points
- + Moderate: 3-4 points
- + Severe degree: 5-6 points

Investigating 105 patients at 2 centers: NIG and HoTM HCMC we noticed that the QOL score after 2 months has been significantly improved: from  $3.54 \pm 0.56$  before treatment to  $2.73 \pm 0.58$  after treatment.

The investigation at NHoTM showed that before treatment there were 40 patients (76.9%) with moderate symptoms, 12 patients (23.1%) with severe symptoms; after treatment the number of patients with mild symptoms had increased significantly: 50 patients (96.2%), and no one had severe symptoms.

### 2.6. *Prostate volume:*

Softgels *Crinum latifolium* have the effect to reduce the prostate volume on ultrasound examination, but at mild degree from  $38.97 \pm 14.32\text{cm}^3$  to  $35.06 \pm 15.01\text{cm}^3$ .

### 2.7. *Volume of residual urine:*

After treatment the average volume of residual urine has reduced from  $18.94\text{cm}^3$  to  $12.27\text{cm}^3$ . The volume of residual urine is a parameter for reference, which is only significant when volume of residual urine  $>50\text{cm}^3$ . This parameter is operator-dependent and depends also on the measurement time.

### 2.8. *Assessment of drug effect on pulse, blood pressure parameters:*

The study on 157 patients at 3 centers showed that:

- Drug did not change significantly the heart rate before and after treatment with  $81.18 \pm 8.06$  cycles/min and  $81.14 \pm 6.23$  cycles/min respectively ( $p>0.05$ ).

- The systolic and diastolic BP did not change significantly with  $p>0.05$ .

## 2.9. *Composite results*

In 157 patients treated with softgels *Crinum latifolium* after 2 months of treatment 140 patients had fairly to good results accounting for 89.18%.

17 patients had poor results (10.82%), with unclear improvement of urination symptoms and prostate volume.

Good results are interpreted as after 2 months of treatment by the drug the clear improvement of urination symptoms has been confirmed, IPSS score was at mild degree <8 points. QOL score decreased, volume of prostate and of residual urine reduced markedly, this group consisted of 70 patients.

Fair results are interpreted as patients have improvement of symptoms, QOL, residual urine, moderate decrease of prostate volume; this group consisted of 70 patients.

In overall the drug is effective for symptomatic improvement, similarly to results reported from study of herbal remedy *Tadenan* by Nguyen Thi Tuyet (7).

## 3. **Discussion about laboratory findings**

### 3.1. *Biochemical findings in blood*

- In limited conditions, we have only conducted the tests for liver function, kidney function by using the parameters such as urea, creatinin, SGOT, SGPT before and after 2 months of treatment.

- Before treatment the urea, creatinin, SGOT, SGPT were 6.07 mmol/l, 102.14 $\mu$ mol/l, 29.03 and 27.08UI/l respectively; after treatment these parameters were 5.86mmol/l, 100.02 $\mu$ mol/l, 30.43 and 26.83UI/l respectively. Thus the softgels *Crinum latifolium* did not change the urea, creatinin, liver enzymes (SGOT, SGPT) with  $p>0.05$ .

### 3.2. *Full blood count:*

- White blood count before treatment was 6.35 thousand/ml, after treatment it was 6.58 thousand/ml, the change was non-significant with  $p>0.5$ . Red blood count increased slightly but remained within normal ranges, 4.418  $\pm$  0.442 before treatment and 4.591  $\pm$  0.376 after 2 months of treatment ( $p<0.05$ ).

- In overall the drug did not significantly influence the full blood count.

### 3.3. *Urinalysis*

- In 55 patients enrolled at NIG we notice:

5 patients had proteinuria  $<0.3\text{g/l}$ . After treatment the amount of proteinuria did not change much. All those 5 have hypertension.

3 patients have hematuria and leucocyturia of non-significant amount.

And we can notice:

Average urine specific density reduced slightly but not significantly with  $p>0.1$

Average urinary pH increased slightly but not significantly with  $p>0.2$

- In 52 patients at NhoTM the changes of urinalysis parameters were not significant with  $p>0.05$

## 4. **Drug side effects**

*Crinum latifolium* is one of herbs which has been longtime used by Vietnamese population and population of many other countries in region for treatment of tumors in uterus and prostate. Based on approval of MOH of Vietnam, we conducted the study on drug safety and side effects. The drug has been tested for assessing the acute toxicity in Research office of Faculty of Traditional Medicine, School of Medicine and Pharmacy Ho Chi Minh City, and achieved the result of  $\text{LD}_{50} = 49.7\text{g/kg}$  of mouse body weight. In August 2003 the semi-chronic toxicity of drug has been tested in NhoTM, and results showed that this drug did not change significantly the biochemical, hematological parameters in rabbits after 2 months of using.

Through 157 studied patients we notice that this drug was relatively safe. 2 patients had suspicion of allergy at the beginning, but after verifying all the factors it was noted that:

+ In one patient at NIG hypertension has been detected during the visits, he started taking anti-hypertensive medication Nifedipine, but previously he usually used the extract of *Crinum latifolium* for treatment of BPH without any event. This patient has been asked to stop Nifedipine, and had anti-histaminic medication for 5 days, then allergic symptoms settled, and he continued to have softgels of *Crinum latifolium* to complete the whole protocol of treatment without allergic manifestation. Thus we could not confirm that the softgels of *Crinum latifolium* caused allergy.

+ In one patient at HoTM HCMC itchy skin rash occurred after starting drug use, this patient has medical history of bronchial asthma, as the allergic manifestations resolved spontaneously 1 day later he can complete the treatment protocol. In this case there is a suspicion of allergy to softgels of Crinum latifolium.

- 4 patients had mild dizziness during the first few days after starting drug use, they adjusted by having more food and the signs improved, thus they did not have to stop treatment.

- 17 patients had some symptoms of GI upset such as abdominal distension, regurgitation of drug odor, thirsty; these symptoms were mild and no one had to stop using drug.

- One patient had insomnia at the beginning but one week later the symptom improved, he did not stop treatment.

In general the side effects of softgels Crinum latifolium were mild and not dangerous.

## **PART 6. CONCLUSION**

Based on results of study conducted on 157 patients who used softgels of Crinum latifolium for treatment of urinary symptoms due to BPH at 3 centers, we can have some conclusions as followings:

### **1. Softgels of Crinum latifolium are effective for treatment of BPH; with results rated as good and fair at 89.18%**

- Clinical symptoms and quality of life of patients improve significantly. Average score IPSS reduced from 19.45 to 7.81 points.

- Drug could reduce the prostate volume but not significantly. Average volume of prostate reduced from 39.87cm<sup>3</sup> to 35cm<sup>3</sup>.

### **2. The drug is safe, with little side effects.**

- Some mild side effects which do not cause discomfort to patients and are only seen in a small number of patients could occur, such as abdominal distension, dizziness, insomnia.

- The paraclinical parameters do not change significantly: urea, creatinin, SGOT, SGPT, full blood count, urinalysis.

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**FRENCH**

**ENGLISH**

<b>MINISTRY OF HEALTH BACH MAI HOSPITAL INSTITUTE OF GERONTOLOGY</b>	
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## **STUDY REPORT**

Full name ..... Age .....  
Address .....

Tel

Date of admission: ...../...../..... Date of treatment ...../...../.....

Date of discharge ...../...../.....

Date of revisit: After 1 month                      After 2 months

Motive of presentation .....

Medical history .....

Previous medication(s): .....

Duration: .....

Diagnosis:

### **FOLLOW-UP CONTENTS**

#### **1. ASSOCIATED DISEASES**

Yes                       No

Disease     

#### **2. DIGITAL RECTAL EXAMINATION**

	Before treatment	After 1 month of treatment	After 2 months of treatment
Consistency			
Surface: smooth, rude, nodular			
Medial fissure			

Aggravation                       Unchanged                       Improvement

#### **3. IPSS SCORE**

	Before treatment	After 1 month of treatment	After 2 months of treatment

Aggravation                       Unchanged                       Improvement

#### 4. QUALITY OF LIFE SCORE

	Before treatment	After 1 month of treatment	After 2 months of treatment

Aggravation

Unchanged

Improvement

#### 5. PROSTATE VOLUME ON ULTRASOUND EXAMINATION

	Before treatment	After 1 month of treatment	After 2 months of treatment

Aggravation

Unchanged

Improvement

#### 6. VOLUME OF RESIDUAL URINE

	Before treatment	After 1 month of treatment	After 2 months of treatment

Aggravation

Unchanged

Improvement

#### 7. SERUM UREA

	Before treatment	After 1 month of treatment	After 2 months of treatment

Aggravation

Unchanged

Improvement

#### 8. SERUM CREATININ

	Before treatment	After 1 month of treatment	After 2 months of treatment

Aggravation

Unchanged

Improvement

#### 9. LIVER ENZYMES

	Before treatment	After 1 month of treatment	After 2 months of treatment
SGOT			
SGPT			

#### 10. FULL BLOOD COUNT

	Before treatment	After 1 month of treatment	After 2 months of treatment
RBC			
Hb			
Hct			
PLT			

### 11. URINALYSIS

	Before treatment	After 1 month of treatment	After 2 months of treatment
RBC			

12. PSA mg/ml

### 13. OTHER SIDE EFFECTS

	Yes	No	Onset
GI upset			
Dizziness, nausea			
Allergy			
Insomnia			
Others			

### ASSESSMENT OF TREATMENT RESULTS

Good       Fair       Moderate, poor

*Reporter*

*Study leader*

**LIST OF PATIENTS PARTICIPATING INTO STUDY**

**LIST OF PATIENTS VOLUNTARILY PARTICIPATING INTO STUDY**

**LIST OF PATIENTS HAVING TREATMENT FOR BPH**