Conprosta and prostatic diseases

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Content

1. Introduction

Prostate diseases have tremendous social and medical importance today; benign prostatic hyperplasia (BPH) is one of the most common chronic diseases in men, while prostate cancer (PCa) is one of the most common malignancies in men.

Beside the great development in the diagnostics and management of prostate diseases, the prevention is of great importance as well. The changes in lifestyle and diet, diet rich in plants and poor in meat, can decrease the risk for many diseases and malignancies.

The action of active substances from Brassica napus pollen contained in Conprosta capsules, on prostate diseases, is presented in this monograph. In addition, basic information about prostate physiology and pathophysiology, are presented.

2. The function of the prostate

Prostate gland is the "crossroad" of genital and urinary ducts in male. The basic function of the prostate is to produce secretions that provide survival and mobility of the spermatozoa.

Prostate appeared in first mammals, some 65 million years ago; today, all mammals have prostate glands, with different shape and size, but similar purpose [1]. In most primates, prostate consists of two lobes, cranial and caudal; prostate in hominids is very much like human [2,3].

Prostate consists of epithelium and stroma; the main epithelial cells are secretory, neuroendocrine, basal and intermediate cells. Stroma consists of fibroblasts, vascular and lymphatic vessels and smooth muscles [4].

One of the most important processes in the prostate is "epithelial-stromal interaction" in which prostatic stroma and epithelium interact and influence on each other. This process starts in embryonic period and lasts during mature period and senium [5].

The most important functions of the prostate are hormonal and secretory. Prostate produces growth factors, like epidermal growth factor (EGF) and fibroblast growth factor (FGF) and androgen hormone dihydrotestosterone (DHT), which acts within the prostate.

Prostatic secretions provide normal pH of seminal fluid and contain glucose, citrate and zinc [6,7]. The most important proteins in prostatic fluid are prostate specific antigen (PSA), glandular kalikrein (hK2) and prostatic acid phosphatase (PAP). At first, PSA has been detected in seminal fluid and urine and later on in the blood. The level of PSA in the blood is essential for the diagnosis of prostate diseases and the follow up during the therapy. The level of PSA in the urine is the potential predictor of BPH progression [8-15].

Figure 1. Epithelial- stromal interaction. E=estrogen, T=testosterone, DHT = dihydrotestosterone, BM = basal membrane, GF = growth factor, 5ar 1= 5 alpha reductase type 1, 5ar 2= 5 alpha reductase type 2, BC = basal cell, SC = secretory cell. (Drawing: Pejčić T, 2013.)

The most important androgen in serum is testosterone (T), while the most important intraprostatic androgen is DHT. After entering into prostatic cell, more than 90% T is converted to DHT, by enzyme 5-alpha reductase (5αR). Both T and DHT are accumulated in the enlarged prostate [16].

The most important serum estrogen in male is estradiol (E2). Almost 90% of E2 in male is produced in peripheral tissues, mainly in adipose tissue, in the reaction of testosterone aromatization. Like androgens, estrogens are accumulated in the prostate, mainly in the prostatic stroma [17]. There are two estrogen receptors in the prostate, ERα and ERβ. The stimulation of ERα increases cell proliferation, while stimulation of ERβ acts in the opposite way [18-21].

Figure 2. Human steroid hormones

3. Benign prostatic hyperplasia

Benign prostatic hyperplasia (BPH) represents progressive enlargement of the prostate, due to formation of new stromal and epithelial cells. It is a chronic disease, followed by weak urinary stream and straining, worsening of the symptoms and complications. The most common complications are chronic infection, stone formation, chronic and acute urinary retention. Except humans, BPH is common in dogs and chimpanzees [22].

The prevalence of BPH in men older than 50 years in USA is 42%, while only 12% in Shanghai. The prevalence is higher in Chinese living in USA [23,24]. These facts suggest that important factors for BPH development are genetic, environmental and related to lifestyle and diet.

BPH is characterized by increasing number of stromal and epithelial cells, due to increased proliferation and decreased programmed cellular death [25]. Older men who develop BPH have decreased serum T and increased E2/T ratio; however, the accumulation of estrogens, T and DHT in the prostate play an important role in BPH development [26-28, 16]. During BPH development, prostate volume increases, approximately 1.9% annually [29]. Gradual prostate enlargement increases urethral resistance, which results in bladder muscle hypertrophy and frequent voiding. Later, bladder muscle gradually decompensates, which is followed by weak urinary stream, chronic and acute urinary retention.

The diagnosis of BPH consists of physical examination, digitorectal examination, ultrasonography and various laboratory tests. In the assessment of symptoms, IPSS (international prostate symptom score) is very useful; uroflowmetry measures patient`s urinary flow and provides objective analysis of the urinary stream.

Figure 3. Benign prostatic hyperplasia. This image is a work of the National Institutes of Health, part of the United States Department of Health and Human Services.

Today, most patients with BPH can be cured with medications; in past few decades the number of surgical procedures decreased dramatically, approximately for 70% [30,31]. At the end of the 20th century, open prostatectomy and transurethral resection of the prostate (TURP), were among the most frequent surgical procedures. Medical therapy includes alpha- adrenergic blockers, 5αR inhibitors and 5-phoshodiesterase inhibitors. Inhibitors of 5αR prevent formation of DHT from testosterone. Finally, various phytotherapeutics emerge as novel potential medications, due to various actions, like anti-inflammatory effect, 5αR inhibition, and effects on growth factors.

4. Prostate cancer

Prostate cancer (PCa) is the second most frequent cancer in males; PCa is very rare in other mammals, including hominids [32].

Global and ethnic differences in PCa are tremendous. In USA, the highest incidence was found in Afro-Americans (220), Caucasians (139), Indians (104) and the lowest in Asians (75) [33]. On the other hand, the lowest incidence was found in rural China (2.6), Eastern Asia (10.5) and Japan (31.2), while it is over 100 in New Zealand and Australia [34,35].

Figure 4. Global prostate cancer incidence

Risk factors for PCa development may be divided to genetic, inflammatory, hormonal and related to lifestyle. Genetic factors are very important: the risk for PCa development is two times higher if father had PCa, and five times higher if both father and brother had PCa [36]. Infections are responsible for about 16% of all cancers [37]. Men with the history of sexually transmitted diseases and prostate infections have increased risk for PCa development [38]. Proliferatory inflammatory atrophy (PIA) in the prostate is frequently followed by PCa [39,40].

The precondition for PCa development is the exposure to androgens in childhood and adulthood. In addition, androgens are essential for PCa survival and growth. Two large studies PCPT (Prostate Cancer Prevention Trial) and REDUCE (Reduction by Dutasteride of Prostate Cancer Events) proved that prolonged use of 5αR inhibitors decreased PCa risk for 25-30% [41].

The estrogens have been traditionally considered protective against PCa. Estrogens act on hypothalamic-pituitary-gonadal axis, increase the levels of SHBG in the serum and hence increase T binding to SHBG. However, it is clear now that estrogens may act as procarcinogens in the prostate [42]. Laboratory mice without ERβ receptors develop PCa; on the contrary, mice without ERα cannot develop PCa.

Disturbances in some cellular signaling pathways may be responsible for the development of some cancers, including PCa. The PI3K/AKT/mTOR pathway is necessary to promote growth and proliferation of adult stem cells. In many cancers, this pathway is overactive, which results in increased proliferation and reduced apoptosis. The PI3K/AKT/mTOR pathway is responsible for the development of hormone-resistant PCa [43].

Fig. 5. PI3K/Akt/mTOR pathway

Lifestyle factors are very important risk factor for PCa. Coffey believes that changes in human diet some 15,000 years ago were responsible for epidemical increase of PCa and breast cancer. Namely, that was the period when man started to build settlements and to cultivate domestic animals. Increased meat intake and decreased plant intake most likely influenced dramatic increase of incidence of those cancers. In fact, it is believed that man was obligatory vegetarian, till late paleolith [44].

Low PCa and breast cancer incidence in Asia may be the result of specific diet: Asians consume much more plants and less meat and fat than Western people [45]. The known fact is that PCa incidence increases in Chinese and Japanese immigrants to USA, compared to their native countries [46-48]. However, in the last decades, meat intake in China has been increased almost 600%, which resulted in the increased incidence of PCa and colon cancer [49].

The treatment of PCa includes numerous surgical and medical modalities. Organ- confined PCa must be cured actively, by radical surgery, or external radiation. Multimodal treatment is indicated for advanced and metastatic disease, and it includes surgery, radiation, hormonal or chemotherapy, depending of the PCa stage and comorbidity.

5. Prostatitis

After BPH and PCa, prostatitis is the third most common urological diagnosis in men over 50 years and the most common urological diagnosis in men younger than 50 years [50]. Overall incidence of prostatitis and chronic pelvic pain syndrome (CPPS) is 7.1% [51]. Prostatic inflammation was seen in 44% prostate specimen after autopsy; however, the cause of prostatitis frequently cannot be recognized [52]. Risk factors for prostatitis are bladder outlet obstruction, intraprostatic ductal reflux and secretory dysfunction of the prostate [53,54].

Acute bacterial prostatitis (ABP) is usually caused by intestinal bacteria, like Escherichia coli (65-80%), while other bacterial species cause 10-15% of infections [55,56]. Some 20% of patients with chronic prostatitis (CP) have antibodies for Chlamydia in the prostatic fluid; however, Chlamydia, as well as Ureaplasma, has never been detected in the prostatic fluid [57]. After the successful treatment of ABP, CBP can persist in following 6-12 months, due to immunological mechanisms. However, reflux of specific substances from the urine into prostatic ducts can cause CBP even in the absence of the pathogenic bacteria [58,59].

Prostatitis syndrome can be divided on four categories: I- ABP, II- CBP, III- CP/CPPS and IV- asymptomatic inflammatory prostatitis [60]. The treatment of prostatitis includes antibiotics, anti-inflammatory drugs, drugs for benign prostatic hyperplasia and phytotherapeutics.

6. Free oxygen radicals, antioxidants and prostatic diseases

Half a century ago, Harman postulated that the main cause of aging and many diseases was the accumulation of reactive oxygen species (ROS) [61]. The most important ROS are hydrogen peroxide, hypochlorous acid, hydroxyl radical and superoxide anion. All ROS can start chain chemical reactions, like oxidation of DNA, oxidation of proteins and peroxidation of lipids, and cause genetic mutations and protein degradation [62]. If the amount of ROS overcomes cellular antioxidative capacity during longer period, oxidative stress (OS) takes place.

The substances that can react with ROS in the cell and thus decrease the oxidative damage of cellular structures are called antioxidants. Human cells can't produce some antioxidants, so they must be taken by plant food, like vitamin C, vitamin E, polyphenols, carotenoids etc. [63]. It is believed that terrestrial plants started with massive antioxidants production in Jurassic, some 200 million years ago, as an adaptation to increased amount of ROS generated during photosynthesis [64].

Diet is very important for OS occurrence; high intake of meat and fat increase oxidative damage, while plant food act protectively [65-67].

7. The effects of Brassica napus pollen on prostate

The plants from genus Brassica are members of Brassicaceae family, or mustard family. The members of the genus Brassica are known as cruciferous vegetable, cabbages, or mustard plants. Today`s species, like Brassica rapa (B. rapa, or B. campestris), B. napus, B. carinata, B. juncea, B. oleracea and B. nigra were created by evolution and chromosomal combinations of the previous species. Brassica napus was created by hybridization of B. rapa and B. oleracea, some 7500 years ago [68]. It is known as rapeseed, rape, oilseed rape, rapa, rappi, rapaseed, canola etc. B napus is yellow flowering plant, used in China and South Africa as vegetable. Brassica napus oil is today on the third place in global oil production, after soya and palm oil [69].

Brassica napus pollen is used as a phytotherapeutic product, due to its content of amino acids, proteins and polyphenols. The pollen can be collected manually, or collected and processed by bees. Pollen consists of many microgametophits, 20-100 μm large. Bees collect pollen on their body and rear legs and transport it in the specific baskets called "corbiculae" [70,71]. The pollen is then transferred to the hive and honeycomb. Bees mix the pollen with their saliva and seal the cell with honey [72].

Fig. 6. Honey bee (Apis mellifera) pollinates rapeseed (Brassica napus) blossom. Valingu, Northwestern Estonia. Author: Ivar Leidus. This file is licensed under the Creative Commons Attribution-Share Alike 4.0 International license.

The composition of pollen differs among different plants and different bees. Usually, sugars make 40-60% of pollen, proteins 20-60%, minerals and vitamins 3%, fatty acids 1-32% and other compounds 5% [73].

Active ingredients in Brassica napus pollen

The most important ingredients of B. napus pollen are proteins, fatty acids, phytosterols, polyphenols and alkaloids. The compounds from pollen act by lot of components, in many phases and cellular processes, of which large number is not fully understood [74].

The major amino acids in B. napus pollen are threonin, valin and methionin; B napus contains 23-24% of raw proteins. Borutinskaitė and coauthors detected over 50 different proteins in B napus, of which one third was unknown [75].

Fatty acids with long chains are one of the most active components of the pollen. It was proven earlier that some unsaturated aliphatic fatty acids have inhibitory effect on enzyme 5αR. Among these acids, gamma- linoleic acid showed the strongest 5αR inhibition on PCa cellular line [76]. In B. rapa pollen, Li detected compounds with potent 5αR inhibitory activity (linoleic acid and monolinolein) and the compounds with potent aromatase inhibitory activity (24-methylenecholesterol linolenate, cycloeucalenol linolenate, 24-methylenecholesterol palmitate, cycloeucalenol, pollinastanol, 24-methylenecholesterol and monopalmitin) [77].

A variety of polyphenols is detected in B napus. Polyphenols are the most abundant secondary metabolites in the plant kingdom, with some 4000 types [78]; their therapeutic properties are known for centuries in the traditional medicine. All polyphenols can be divided to flavonoids and non-flavonoids. According to Linus Pauling Institute, polyphenols from the food have low direct antioxidative activity after ingestion; it is more likely that the increase of the plasma antioxidative capacity is the consequence of increased plasma levels of uric acid [79]. In addition, polyphenols increase the expression of enzyme paraoxonase, which prevents LDL (low density lipoprotein) oxidation [80,81]. The absorption of polyphenols is variable and depends of the amount and the molecular weight of the phenolic compound, previous food ingestion, gender and the differences in gut microflora [82].

Many researchers proved antioxidant and apoptotic activity of polyphenols in isolated prostate cancer cell lines.

Han showed that extract of B. napus pollen showed strong activity in decreasing the secretion of PSA in LNCaP cells. His team isolated five flavonoids from the extract of B napus pollen: naringenin, luteolin, kaempferol, kaempferol 3-(3-E-p-coumaroyl-alpha-L-rhamnopyranoside) and kaempferol 3-(2,3-di-E-p-coumaroyl-alpha-L-rhamnopyranoside) [83].

In the bee honey from B rapa, Guo isolated the next polyphenols: kaemferol-3-O-beta-D-glucosyl-(2-->1)-beta-D-glucoside, kaemferol-3,4'-di-O-beta-D-glucoside and quercetin-3-O-beta-D-glucosyl-(2-->1)-beta-D-glucoside. Other compounds from the bee honey were β-sitosterol, nicotinic acid, nicotinamide, trans-p-coumaric acid-4-O-beta-D-glucopyranoside and 5-hydroxymethylfurfural [84].

Fang profiled 18 phenolic compounds from an ethanol extract of rapeseed: two major phenols, sinapine and methyl sinapate, and 16 minor phenolic compounds, from which seven were new lignans [85]. Qu found that epicatechin, quercetin, isorhamnetin and kaempferol were present in higher concentrations in black-seeded, than in yellow-seeded B. napus [86].

In B. napus seeds, Shao detected 61 flavonoids (39 kaempferol derivatives, 11 isorhamnetin derivatives, 5 quercetin derivatives, 6 flavanols) and 30 hydroxycinnamic acid derivatives [87].

In the recent research, Li used the new approach, liquid chromatography-diode array detector-electrospray ionization-mass spectrometry, combined with nuclear magnetic resonance technology, to identify flavonoids in B. napus bee pollen. Four compounds were identified: quercetin-3-O-β-D-glucosyl-(2→l)-β-glucoside, kaempferol-3, 4'-di-O-β-D-glucoside, 5, 7, 4'-trihydroxy-3'-methoxyflavone-3-O-β-D-sophoroside and kaempferol-3-O-β-D-glucosyl-(2→l)-β-D-glucoside [88].

Phytosterols are present primarily in the seed of B napus; their known activities in human body are anti-inflammatory activity, induction of apoptosis, induction of angiogenesis and the reduction of serum cholesterol levels [89,90]. Holtz demonstrated that β-sitosterol, in concentration of 16μM, suppressed cell proliferation in LNCaP (lymph node metastatic lesion of prostatic adenocarcinoma) cells, and induced cell apoptosis [91]. Similarly, Wu demonstrated that steroid fraction from B. napus and B. campestris induced apoptosis and increased caspase-3 activity [92]. (Activation of caspases plays a central role in cell apoptosis). Phytosterol brassinolide from B napus is particularly active on androgen refractory PCa cells, and lesser on androgen sensitive, LNCaP cells [93].

Finally, low amounts of epicatechin and some lignans were detected in Brassica plants [94,95].

In vitro studies of Brassica napus pollen activity

In 2007, Han showed that pollen extract of B. napus showed strong activity in decreasing the secretion of PSA in LNCaP cells [83].

Other authors also reported that active components of B. napus pollen, like kaempferol and quercetin, inhibit proliferation of PCa cells. In 2008, Bandyopadhyay found that kaempferol and quercetin activate immunologic response in PCa cells, by stimulating Granulocyte-macrophage colony-stimulating factor production [96].

In 2015, Halimah found that kaempferol-3-O-rhamnoside inhibits proliferation of LNCaP cells, by increasing the expression of caspase 3, 8 and 9 [97]. It is interesting that quercetin in combination with metformin, inhibits growth, migration and invasion on PC-3 and LNCaP cells, by inhibition of VEGF/Akt/PI3K signaling pathway [98].

Naringenin and luteolin were also detected in B napus pollen [83]. In 2017, Lim proved that naringenin inhibited proliferation and migration of cells in PC-3 and LNCaP lines and simultaneously activated its apoptosis [99]. Luteolin inhibited proliferation and migration of PCa cells [100].

Hydroxycinnamic acid was also detected in rapeseed [Fang][Fang]. Szliszka found that hydroxycinnamic acids together with propolis extract showed cytotoxic and apoptotic activity in LNCaP and DU-145 prostate cancer cells [101].

Animal studies

In 2013, Li proved the improvement of BPH in mice fed with B napus pollen. Prostatic hyperplasia was induced with T injections and prolonged laboratory stress. After 14 days, measurements showed prostatic enlargement, elevated serum T and increased activity of 5αR and acid phosphatase. The improvement of BPH was better in the combination of rape pollen and anthocyanins from blueberry [102].

In 2013, Jafarian-Dehkordi proved that B. rapa extract decreased inflammation in mouse [103].

In 2014, on the rat model, Yang proved that bee collected rape pollen caused regression of prostatic epithelium and the decrease of serum and tissue levels of T and DHT. In the rat model, BPH was induced by daily subcutaneous injections of T. After 30 days, increased levels of T and DHT and increased prostatic volume were detected. In addition, increased expression of 5αR-1, 5αR-2 and cyclooxygenase-2 (COX-2) were detected. (Inhibition of COX provides the relief of pain and inflammation [104]). Rape pollen was administered orally, at the same time with T injections. In the group of animals treated with pollen, significant decrease of 5αR and COX expression were detected, together with the decrease of T and DHT levels and the decrease of prostatic volume [105].

In 2015, Zou proved that rats fed with B napus honey tablets (Pulean) had weaker prostate inflammation. The model of chronic abacterial prostatitis was created after the animals were castrated and consequently given the injection of estradiol. After eight days, animals were fed with Pulean by gastrogavage. In rats fed with Pulean, inflammatory reaction was modest; in addition, decreased levels of inflammatory factors IL-1β, IL-10, i TNF-α were detected [106].

It was proven that B. napus pollen ingested orally, can be detected in mouse serum. In 2015, Chen detected micro RNA (miRNA) from B. napus pollen in mouse serum: in the issue from 2018, the same authors detected miRNA in the posterior prostate lobes in rats and the improvement of BPH symptoms. The authors concluded that B. napus pollen can be absorbed in the mouse blood and can cross blood-prostatic barrier [107,108].

Human studies

In 2008, Fu found significant improvement of BPH symptoms in patients taking Conprata Pulean tablets, made of B. napus bee honey. After three months of therapy, 60 patients reported improvement in IPSS questionnaire and Qmax during uroflowmetry [109].

In 2011, Yue found that treatment with Pulean tablets (Qian Likang) significantly improved BPH symptoms on IPSS and increased urine flow. Both symptoms and uroflowmetry parameters significantly improved after 30 days of therapy and continued to improve during following 90 days [110].

In 2013, Zhu found symptoms improvement in 240 patients with BPH treated with Pulean during two years. The improvement was slightly lower than in the group of patients treated with 5αR inhibitors [111].

Conclusion

The diseases of the prostate gland have great medical and social significance in the modern world. Benign prostatic hyperplasia is one of the commonest chronic diseases in men; prostate cancer is the leading cancer in the Western world, while large number of younger men suffers from prostate inflammations.

The present time is characterized by the great advances in diagnostic, therapeutical and technological improvements in the treatment of prostatic diseases. The wide use of laboratory tests like PSA as well as the use of ultrasound and magnetic resonance etc, dramatically improved the detection of various prostatic diseases. Finally, modern surgical procedures and the development of laparoscopic and robotic procedures significantly improved the cure rates in the prostate cancer patients.

However, the prevention of prostatic diseases is important almost as the modern therapy. The experiences from the traditional medicine, as well as large epidemical studies, show that specific phytotherapeutic products, together with the lifestyle and diet, can decrease the risk from prostatic diseases.

Figure 7. Conprosta

The therapeutic properties of Brassica napus pollen are known for the long time in the Chinese traditional medicine. However, modern laboratory researches and epidemiological studies also confirm positive effects of B. napus pollen on prostatic inflammations, BPH and prostate cancer.

Dry extract of B napus pollen is present in Conprosta capsules in the dose of 500 mg, and 600 mg in Conprosta Forte. Recommended dose is two capsules daily, one in the morning and one in the evening.

References

1. Furumura K, Kuriki T, Miyazaki S. Growth and sexual maturation of the male house musk shrew (Suncus murinus) Jikken Dobutsu. 1984 Apr;33(2):193-200.

2. Lewis RW, Kim JC, Irani D, Roberts JA. The prostate of the nonhuman primate: normal anatomy and pathology. Prostate. 1981;2(1):51-70.

3. Blacklock NJ, Bouskill K. The zonal anatomy of the prostate in man and in the rhesus monkey (Macaca mulatta). Urol Res. 1977;5(4):163-7.

4. Miner JH, Yurchenco PD. Laminin functions in tissue morphogenesis. Annu Rev Cell Dev Biol. 2004;20:255-84.

5. Berman DM, Rodriguez R, Veltri RW. Development, Molecular Biology, and Physiology of the Prostate. In: Wein AJ, Kavoussi LR, Partin AW, Peters CA and Novick AC, editors. Campbell- Walsh Urology, 10th ed. Philadelphia: Saunders, 2012. Section 16, Chapt 90, pp. 2533- 2569

6. Serkova NJ, Gamito EJ, Jones RH, O'Donnell C, Brown JL, Green S, Sullivan H, Hedlund T, Crawford ED. The metabolites citrate, myo-inositol, and spermine are potential age-independent markers of prostate cancer in human expressed prostatic secretions. Prostate. 2008 May 1;68(6):620-8.

7. Costello LC, Franklin RB. The clinical relevance of the metabolism of prostate cancer; zinc and tumor suppression: connecting the dots. Mol Cancer. 2006 May 15;5:17.

8. Pejcic T, Hadzi-Djokic J, Acimovic M, Topuzovic C, Milkovic B, Janjic A. Urinary prostate specific antigen: is the clinical use likely? Acta Chir Iugosl. 2005;52(4):69-74.

9. Tomislav P. Pejčić. Prostata specifični antigen u urinu. Zadužbina Andrejević, Beograd, 2005.

10. T. Pejcic, J. Hadzi-Djokic, R. Radosavljevic, L. Hajdukovic, B. Milkovic. Can urinary PSA determination improve T-staging of prostate cancer? Urology, Volume 68, Issue null, 2006; Pages 272-272

11. Pejcić T, Hadzi-Djokić J, Marković B, Dragićević D, Glisić B, Lalić N, Aćimović M, Dzamić Z, Radosavljevic R. Urinary PSA level and relative tumor volume after prostate biopsy. Acta Chir Iugosl. 2009;56(2):17-21.

12. Pejcić T, Hadzi-Djokić J, Marković B, Lalić N, Glisić B. What are the possible reasons for urethral PSA varieties after radical prostatectomy? Acta Chir Iugosl. 2010;57(2):31-5.

13. Pejcic T, Hadzi-Djokić J, Topuzović C, Basić D, Marjanović A, Djurasic L. The analysis of some factors that influence on serum PSA level in localized prostate cancer patients: mathematical model. Acta Chir Iugosl. 2011;58(1):81-7.

14. Pejcić T, Dimitrijević V, Hadzi-Djokić J. Urinary PSA in monitoring of patients with prostate cancer. Acta Chir Iugosl. 2012;59(1):57-60.

15. Pejcic TP, Tulic CDz, Lalic NV, Glisic BD, Ignjatovic SD, Markovic BB, Hadzi-Djokic JB. Urinary prostate-specific antigen: predictor of benign prostatic hyperplasia progression? Can J Urol. 2013 Apr;20(2):6707-13.

16. Pejčić T, Tosti T, Tešić Ž, Milković B, Dragičević D, Kozomara M, Čekerevac M, Džamić Z. Testosterone and dihydrotestosterone levels in the transition zone correlate with prostate volume. Prostate. 2017 Jul;77(10):1082-1092.

17. Kozák I, Bartsch W, Krieg M, Voigt KD. Nuclei of stroma: site of highest estrogen concentration in human benign prostatic hyperplasia. Prostate. 1982;3(5):433-8.

18. Tsurusaki T, Aoki D, Kanetake H, Inoue S, Muramatsu M, Hishikawa Y, et al. Zone-dependent expression of estrogen receptors alpha and beta in human benign prostatic hyperplasia. J Clin Endocrinol Metab 2003;88:1333-40.

19. Fixemer T, Remberger K, Bonkhoff H. Differential expression of the estrogen receptor beta (ERbeta) in human prostate tissue, premalignant changes, and in primary, metastatic, and recurrent prostatic adenocarcinoma. Prostate 2003;54:79-87.

20. Dahlman-Wright K, Cavailles V, Fuqua SA, Jordan VC, Katzenellenbogen JA, Korach KS, Maggi A, Muramatsu M, Parker MG, Gustafsson JA.International Union of Pharmacology. LXIV. Estrogen Receptors. Pharmacol Rev. 2006; 58:773–781.

21. Heldring N, Pike A, Andersson S, Matthews J, Cheng G, Hartman J, Tujague M, Strom A, Treuter E, Warner M, Gustafsson JA. Estrogen receptors: how do they signal and what are their targets. Physiological Reviews.2007; 87:905–931.

22. Moore RJ, Gazak JM, Quebbeman JF, Wilson JD. Concentration of dihydrotestosterone and 3 alpha-androstanediol in naturally occurring and androgen-induced prostatic hyperplasia in the dog. J Clin Invest. 1979 Oct;64(4):1003-10.

23. Lee SWH, Chan EMC, Lai YK. The global burden of lower urinary tract symptoms suggestive of benign prostatic hyperplasia: A systematic review and meta-analysis. Sci Rep. 2017;7(1):7984.

24. Platz EA, Kawachi I, Rimm EB, Willett WC, Giovannucci E. Race, ethnicity and benign prostatic hyperplasia in the health professionals follow-up study. J Urol. 2000 Feb;163(2):490-5.

25. Isaacs JT. Prostate stem cells and benign prostatic hyperplasia. Prostate. 2008 Jun 15;68(9):1025-34.

26. Kozák I, Bartsch W, Krieg M, Voigt KD. Nuclei of stroma: site of highest estrogen concentration in human benign prostatic hyperplasia. Prostate 1982;3:433-8.

27. Marberger M, Roehrborn CG, Marks LS, Wilson T, Rittmaster RS. Relationship among serum testosterone, sexual function, and response to treatment in men receiving dutasteride for benign prostatic hyperplasia. J Clin Endocrinol Metab. 2006 Apr;91(4):1323-8.

28. Roberts RO, Jacobson DJ, Rhodes T, Klee GG, Leiber MM, Jacobsen SJ. Serum sex hormones and measures of benign prostatic hyperplasia. Prostate. 2004 Oct 1;61(2):124-31

29. Rhodes T, Girman CJ, Jacobsen SJ, Roberts RO, Guess HA, Lieber MM. Longitudinal prostate growth rates during 5 years in randomly selected community men 40 to 79 years old. J Urol. 1999 Apr;161(4):1174-9.

30. McVary KT. A review of combination therapy in patients with benign prostatic hyperplasia. Clin Ther. 2007 Mar;29(3):387-98.

31. Mebust WK, Holtgrewe HL, Cockett AT, Peters PC; Writing Committee, the American Urological Association. Transurethral prostatectomy: immediate and postoperative complications. Cooperative study of 13 participating institutions evaluating 3,885 patients. J Urol, 141: 243-247, 1989. J Urol. 2002 Jan;167(1):5-9.

32. Pejčić TP. Evolucija prostate. U: Pejčić TP, Hadži-Đokić JB, Bašić DT. Prostata. Beograd: Elit Medica; 2014.

33. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014 Jan-Feb;64(1):9-29.

34. Chen, R., Ren, S., Yiu, M. K., Fai, N. C., Cheng, W. S., Ian, L. H., ... & Chiu, J. Y. (2014). Prostate cancer in Asia: a collaborative report. Asian Journal of Urology, 1(1), 15-29.

35. Baade PD, Youlden DR, Cramb SM, Dunn J, Gardiner RA. Epidemiology of prostate cancer in the Asia-Pacific region. Prostate Int. 2013;1(2):47-58.

36. Zeegers MP, Jellema A, Ostrer H. Empiric risk of prostate carcinoma for relatives of patients with prostate carcinoma: a meta-analysis. Cancer 2003; 97:1894–903

37. de Martel C, Ferlay J, Franceschi S, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. Lancet Oncol 2012;13:607–15.

38. Cheng I, Witte JS, Jacobsen SJ, et al. Prostatitis, sexually transmitted diseases, and prostate cancer: the California Men's Health Study. PLoS One 2010;5:e8736.

39. De Marzo AM, Platz EA, Sutcliffe S, et al. Inflammation in prostate carcinogenesis. Nat Rev Cancer 2007;7:256–69.

40. Nelson WG, De Marzo AM, Isaacs WB. Prostate cancer. N Engl J Med 2003;349:366–81.

41. Andriole G, Bostwick DG, Brawley OW, et al. Effect of dutasteride on the risk of prostate cancer. N Engl J Med 2010;362:1192–202.

42. Hu WY, Shi GB, Lam HM, et al. Estrogen-initiated transformation of prostate epithelium derived from normal human prostate stem-progenitor cells. Endocrinology 2011;152:2150–63.

43. Edlind MP, Hsieh AC. PI3K-AKT-mTOR signaling in prostate cancer progression and androgen deprivation therapy resistance. Asian J Androl. 2014 May-Jun;16(3):378-86.

44. Coffey DS. Similarities of prostate and breast cancer: Evolution, diet, and estrogens. Urology. 2001 Apr;57(4 Suppl 1):31-8.

45. K.C. Nam, C. Jo, M. Lee. Meat products and consumption culture in the East. Meat Sci, 86 (2010), pp. 95-102

46. Yu H, Harris RE, Gao YT, Gao R, Wynder EL. Comparative epidemiology of cancers of the colon, rectum, prostate and breast in Shanghai, China versus the United States. Int J Epidemiol. 1991 Mar;20(1):76-81.

47. Shimizu H, Ross RK, Bernstein L, et al. Cancers of the prostate and breast among Japanese and white immigrants in Los Angeles county. Br J Cancer 1991;63:963–6.

48. Bostwick DG, Burke HB, Djakiew D, et al. Human prostate cancer risk factors. Cancer 2004;101:2371–490.

49. J. Zhang, I.B. Dhakal, Z. Zhao, L. Li. Trends in mortality from cancers of the breast, colon, prostate, esophagus, and stomach in East Asia: role of nutrition transition. Eur J Cancer Prev, 21 (2012), pp. 480-489

50. Collins MM, Stafford RS, O'Leary MP, Barry MJ. How common is prostatitis? A national survey of physician visits. J Urol. 1998 Apr;159(4):1224-8.

51. Pontari MA, Joyce GF, Wise M, McNaughton-Collins M; Urologic Diseases in America Project. Prostatitis. J Urol. 2007 Jun;177(6):2050-7.

52. Nickel JC. Inflammatory and Pain Conditions of the Male Genitourinary Tract: Prostatitis and Related Pain Conditions, Orchitis, and Epididymitis. In: Wein AJ, Kavoussi LR, Partin AW and Peters CA, editors. Campbell- Walsh Urology, 11th ed. Philadelphia: Elsevier, 2016. Part III, Chapt 12, pp. 304-333 e6.

53. Ghobish A. Voiding dysfunction associated with "chronic bacterial prostatitis".Eur Urol. 2002 Aug;42(2):159-62.

54. Kirby RS, Lowe D, Bultitude MI, Shuttleworth KE. Intra-prostatic urinary reflux: an aetiological factor in abacterial prostatitis. Br J Urol. 1982 Dec;54(6):729-31.

55. Schneider H, Ludwig M, Weidner W, Brähler E. Experience with different questionnaires in the management of patients with CP/CPPS: GPSS, IPSS and NIH-CPSI. World J Urol. 2003 Aug;21(3):116-8

56. Weidner W, Schiefer HG, Krauss H, Jantos C, Friedrich HJ, Altmannsberger M. Chronic prostatitis: a thorough search for etiologically involved microorganisms in 1,461 patients. Infection. 1991;19 Suppl 3:S119-25.

57. Shortliffe LM, Sellers RG, Schachter J. The characterization of nonbacterial prostatitis: search for an etiology. J Urol. 1992 Nov;148(5):1461-6.

58. Fowler JE Jr, Mariano M. Longitudinal studies of prostatic fluid immunoglobulin in men with bacterial prostatitis. J Urol. 1984 Feb;131(2):363-9.

59. Quick ML, Wong L, Mukherjee S, Done JD, Schaeffer AJ, Thumbikat P. Th1-Th17 cells contribute to the development of uropathogenic Escherichia coli-induced chronic pelvic pain. PLoS One. 2013;8(4):e60987.

60. Shoskes DA, Landis JR, Wang Y, Nickel JC, Zeitlin SI, Nadler R; Chronic Prostatitis Collaborative Research Network Study Group. Impact of post-ejaculatory pain in men with category III chronic prostatitis/chronic pelvic pain syndrome. J Urol. 2004 Aug;172(2):542-7.

61. Harman D. The biologic clock: the mitochondria? J Am Geriatr Soc. 1972 Apr;20(4):145-7.

62. D'Andrea GM. Use of antioxidants during chemotherapy and radiotherapy should be avoided. CA Cancer J Clin. 2005 Sep-Oct;55(5):319-21.

63. Sies H. Oxidative stress: oxidants and antioxidants. Exp Physiol. 1997 Mar;82(2):291-5.

64. Aggarwal BB, Shishodia S (May 2006). "Molecular targets of dietary agents for prevention and therapy of cancer". Biochemical Pharmacology. 71 (10): 1397–421.

65. Hodgson JM, Ward NC, Burke V, Beilin LJ, Puddey IB. Increased lean red meat intake does not elevate markers of oxidative stress and inflammation in humans. J Nutr. 2007 Feb;137(2):363-7.

66. Halliwell B, Chirico S. Lipid peroxidation: its mechanism, measurement, and significance. Am J Clin Nutr. 1993 May;57(5 Suppl):715S-724S; discussion 724S-725S.

67. Orlich MJ, Singh PN, Sabaté J, Fan J, Sveen L, Bennett H, Knutsen SF, Beeson WL, Jaceldo-Siegl K, Butler TL, Herring RP, Fraser GE. Vegetarian dietary patterns and the risk of colorectal cancers. JAMA Intern Med. 2015 May;175(5):767-76.

68. Chalhoub B, Denoeud F, Liu S, Parkin IA, Tang H, Wang X, et al. Plant genetics. Early allopolyploid evolution in the post-Neolithic Brassica napus oilseedgenome. Science. 2014 Aug 22;345(6199):950-3.

69. https://www.worldatlas.com/articles/the-world-s-top-rapeseed-producing-countries.html

70. Microbiology of pollen and bee bread: the yeasts". Apidologie. 10: 45–53.

71. Mutsaers, Marieke; van Blitterswijk, Henk; van't Leven, Leen; Kerkvliet, Jaap; van de Waerdt, Jan (2005). Bee products properties, processing and marketing (PDF). Wageningen: Agromisa Foundation. pp. 34–35.

72. "Examination of "pollen Balls" in the Nests of the Alfalfa Leafcutting Bee, Megachile Rotundata". United States Department of Agriculture. Agricultural Research Service. Retrieved 10 September 2011.

73. Staff writer (September 2011). "What Is Bee Bread?". Keeping-Honey-Bees.com. Archived from the original on 11 July 2016.

74. Sun Yi, Yang Yifang, Yang Bicheng, Chen Qiongshan. Advances in studies on physiological activities and mechanisms of Bee Pollen of Brassica campestris. Apiculture of China; 2010-09.

75. Borutinskaitė V, Treigytė G, Matuzevičius D, Zaikova I, Čeksterytė V, Navakauskas D, Kurtinaitienė B, Navakauskienė, R. Proteomic Analysis of Pollen and Blossom Honey from Rape Seed Brassica Napus L. J. Apic. Sci. Vol. 61 No I, 2017.

76. Liang T, Liao S. Inhibition of steroid 5 alpha-reductase by specific aliphatic unsaturated fatty acids. Biochem J. 1992 Jul 15;285 (Pt 2):557-62.

77. Li YH, Yang YF, Li K, Jin LL, Yang NY, Kong DY. 5 alpha-reductase and aromatase inhibitory constituents from Brassica rapa L. pollen. Chem Pharm Bull (Tokyo). 2009 Apr;57(4):401-4.

78. Rasines-Perea Z, Teissedre PL.
Grape Polyphenols' Effects in Human Cardiovascular Diseases and Diabetes. Molecules. 2017 Jan 1;22(1). pii: E68.

79. Lotito SB, Frei B. Consumption of flavonoid-rich foods and increased plasma antioxidant capacity in humans: cause, consequence, or epiphenomenon? Free Radic Biol Med. 2006 Dec 15;41(12):1727-46. Epub 2006 Jun 3.

80. Ng CJ, Wadleigh DJ, Gangopadhyay A, et al. (November 2001). "Paraoxonase-2 is a ubiquitously expressed protein with antioxidant properties and is capable of preventing cell-mediated oxidative modification of low density lipoprotein". J. Biol. Chem. 276 (48):

81. Khateeb J, Gantman A, Kreitenberg AJ, Aviram M, Fuhrman B. Paraoxonase 1 (PON1) expression in hepatocytes is upregulated by pomegranate polyphenols: a role for PPAR-gamma pathway. Atherosclerosis. 2010 Jan;208(1):119-25.

82. Anhê, F.F.; Desjardins, Y.; Pilon, G.; Dudonné, S.; Genovese, M.I.; Lajolo, F.M.; Marette, A. Polyphenols and type 2 diabetes: A prospective review. PharmaNutrition2013, 1, 105–114.

83. Han HY, Shan S, Zhang X, Wang NL, Lu XP, Yao XS. Down-regulation of prostate specific antigen in LNCaP cells by flavonoids from the pollen of Brassica napus L. Phytomedicine. 2007 May;14(5):338-43. Epub 2006 Nov 7.

84. Guo J, Zhang P, Zhang Z. Studies on chemical constituents from bee-collected rape pollen. Zhongguo Zhong Yao Za Zhi. 2009 May;34(10):1235-7.

85. Fang J, Reichelt M, Kai M, Schneider B. Metabolic profiling of lignans and other secondary metabolites from rapeseed (Brassica napus L.). J Agric Food Chem. 2012 Oct 24;60(42):10523-9.

86. Qu C, Fu F, Lu K, Zhang K, Wang R, Xu X, Wang M, Lu J, Wan H, Zhanglin T, Li J. Differential accumulation of phenolic compounds and expression of related genes in black- and yellow-seeded Brassica napus. J Exp Bot. 2013 Jul;64(10):2885-98.

87. Shao Y, Jiang J, Ran L, Lu C, Wei C, Wang Y. Analysis of flavonoids and hydroxycinnamic acid derivatives in rapeseeds (Brassica napus L. var. napus) by HPLC-PDA--ESI(--)-MS(n)/HRMS. J Agric Food Chem. 2014 Apr 2;62(13):2935-45.

88. Li Y, Qi Y, Ritho J, Zhang Y, Zheng X, Zhou J, Sun L. Characterization of flavonoid glycosides from rapeseed bee pollen using a combination of chromatography, spectrometry and nuclear magnetic resonance with a step-wise separation strategy. Nat Prod Res. 2016;30(2):228-31.

89. Chai JW, Kuppusamy UR, Kanthimathi MS. Beta-sitosterol induces apoptosis in MCF-7 cells. Malays J Biochem Molecular Bio. 2008;16:28-30.

90. Soodabeh S, Azadeh M, Ahmad RG, Mohammad A. The Story of Beta-sitosterol- A Review. European Journal of Medicinal Plants. 2014 May; 4(5): 590-609.

91. Holtz RL, Fink CS, Awad AB. Beta-sitosterol activates the sphingomyelin cycle and induces apoptosis in LNCaP human prostate cancer cells. Nutr Cancer. 1998;32:8-12.

92. Wu YD, Lou YJ. A steroid fraction of chloroform extract from bee pollen of Brassica campestris induces apoptosis in human prostate cancer PC-3 cells. Phytother Res. 2007 Nov;21(11):1087-91.

93. Wu YD, Lou YJ. Brassinolide, a plant sterol from pollen of Brassica napus L., induces apoptosis in human prostate cancer PC-3 cells. Pharmazie. 2007 May;62(5):392-5.

94. "Lignans". Micronutrient Information Center, Linus Pauling Institute, Oregon State University. 2010. Retrieved 31 July2017.

95. Milder IE, Arts IC, van de Putte B, Venema DP, Hollman PC (2005). "Lignan contents of Dutch plant foods: a database including lariciresinol, pinoresinol, secoisolariciresinol and matairesinol". Br. J. Nutr. 93 (3): 393–402.

96. Bandyopadhyay S, Romero JR, Chattopadhyay N. Kaempferol and quercetin stimulate granulocyte-macrophage colony-stimulating factor secretion in human prostate cancer cells. Mol Cell Endocrinol. 2008 Jun 11;287(1-2):57-64.

97. Halimah E, Diantini A, Destiani DP, Pradipta IS, Sastramihardja HS, Lestari K, Subarnas A, Abdulah R, Koyama H. Induction of caspase cascade pathway by kaempferol-3-O-rhamnoside in LNCaP prostate cancer cell lines. Biomed Rep. 2015 Jan;3(1):115-117. Epub 2014 Nov 14.

98. Sun S, Gong F, Liu P, Miao Q. Metformin combined with quercetin synergistically repressed prostate cancer cells via inhibition of VEGF/PI3K/Akt signaling pathway. Gene. 2018 Jul 20;664:50-57.

99. Lim W, Park S, Bazer FW, Song G. Naringenin-Induced Apoptotic Cell Death in Prostate Cancer Cells Is Mediated via the PI3K/AKT and MAPK Signaling Pathways. J Cell Biochem. 2017 May;118(5):1118-1131.

100. Han K, Lang T, Zhang Z, Zhang Y, Sun Y, Shen Z, Beuerman RW, Zhou L, Min D. Luteolin attenuates Wnt signaling via upregulation of FZD6 to suppress prostate cancer stemness revealed by comparative proteomics. Sci Rep. 2018 Jun 4;8(1):8537.

101. Szliszka E, Czuba ZP, Bronikowska J, Mertas A, Paradysz A, Krol W. Ethanolic Extract of Propolis Augments TRAIL-Induced Apoptotic Death in Prostate Cancer Cells. Evid Based Complement Alternat Med. 2011;2011:535172.

102. Yi-Fang Li , Lu-PingTang, Rong-Rong He, Zhe Xu, Qiong-Qiong He, Fei-Jun Xiang, Wei-Wei Su, Hiroshi Kurihara. Anthocyanins extract from bilberry enhances the therapeutic effect of pollen

of Brassica napus L. on stress-provoked benign prostatic hyperplasia in restrained mice. Journal of Functional Foods. Volume 5, Issue 3, July 2013, Pages 1357-1365.

103. Jafarian-Dehkordi A, Zolfaghari B, Mirdamadi M. The effects of chloroform, ethyl acetate and methanolic extracts of Brassica rapa L. on cell-mediated immune response in mice. Res Pharm Sci. 2013 Jul;8(3):159-65.

104. Litalien C, Beaulieu P Molecular Mechanisms of Drug Actions: From Receptors to Effectors. Chapter 117. In Fuhrman BP, Zimmerman JJ. Pediatric Critical Care (4th ed.). Philadelphia, PA: Elsevier Saunders (2011). pp. 1553–1568.

105. Yang BC, Jin LL, Yang YF, Li K, Peng DM.
Inhibitory effect of rape pollen supercritical CO2 fluid extract against testosterone-induced benign prostatic hyperplasia in rats. Exp Ther Med. 2014 Jul;8(1):31-37.

106. Zou RZ, Cao JG, Feng QZ, Sun JQ. Effect of Qianlean Pill on IL-1β, IL-10, and TNF-α in Prostate Tissues of Chronic Nonbacterial Prostatitis Rats. Zhongguo Zhong Xi Yi Jie He Za Zhi. 2015 Oct;35(10):1223-7.

107. Chen X, Dai GH, Ren ZM, Tong YL, Yang F, Zhu YQ. Identification of Dietetically Absorbed Rapeseed (Brassica campestris L.) Bee Pollen MicroRNAs in Serum of Mice. Biomed Res Int. 2016;2016:5413849.

108. Chen X, Wu RZ, Zhu YQ, Ren ZM, Tong YL, Yang F, Dai GH. Study on the inhibition of Mfn1 by plant-derived miR5338 mediating the treatment of BPH with rape bee pollen. BMC Complement Altern Med. 2018 Jan 30;18(1):38.

109. FU Wei-jun,HE Xue-you, SHI Li-xin, WANG Xi-you, HONG Bao-fa, GAO Jiang-ping, ZHANG Lei, YANG Yong, SHONG Tao. Clinical observation on therapeutic efficiency of conprata pulean in the treatment of benign prostate hyperplasia. Academic Journal of PLA Postgraduate Medical School, 2008-01

110. ZHOU Yue, WU Hai-xiao. Relationship between clinical efficacy and treatment course of Pule'an Pian used in benign prostatic hypertrophy. Chinese Traditional and Herbal Drugs; 2011-08.

111. ZHU Cun-hai, YE Chang, WANG Jin-en, SONG Yong-bo, LIU Xiao-bing. Drug treatment for benign prostatic hyperplasia. Journal of Hainan Medical University. 2013-04.