

# Botanicals and Nutrients to Decrease BPH Symptoms and Optimize Prostate Health

Co-authored by Donald R. Yance, RH (AHG), CN  
and Suzanne E. Sky, L.Ac., MTOM

## Discussion

The prostate, a small gland about the size of a walnut in healthy young men, is found just below the bladder and in front of the rectum. Prostate enlargement often occurs in men over age 40 and, at some point, more than half of these aging men develop benign prostatic hyperplasia (BPH) with symptoms and changes in the prostate tissue. Since it surrounds the urethra, a swollen prostate gland often causes urinary issues that vary with frequency and intensity. About one-third of men experience some urinary difficulties associated with BPH by age 50. By age 80, about 90% of all men experience some degree of BPH which is characterized by proliferation of smooth muscle and epithelial cells, causing enlargement of the prostate.<sup>1</sup>

Multiple shifts in prostate androgen metabolism are contributing factors to BPH. As men age androgen levels naturally decline, influencing the estrogen/androgen ratio in favor of estrogens along with other changes that vary by individual. Studies estimate that total testosterone levels begin to shift around age 45 to 50 years of age.<sup>1</sup>

High androgen concentrations in the prostate support its main function, which is secretion of fluids essential for reproduction. It is hypothesized that prostate tissue is adversely affected over time by these high concentration of androgens, especially by the powerful androgen 5-alpha-dihydrotestosterone (DHT).<sup>2,3</sup> While DHT helps support homeostasis between cell proliferation and cell death,<sup>3</sup> higher conversion of testosterone to DHT by 5-alpha-reductase in the prostate can result in increased cell proliferation.<sup>1</sup>

Many of the botanicals and natural compounds highlighted in this paper target the 5-alpha-reductase enzyme pathway, thus inhibiting over-production of DHT. At the same time, these plant extracts and nutrients work through several pathways to support optimal prostate function.

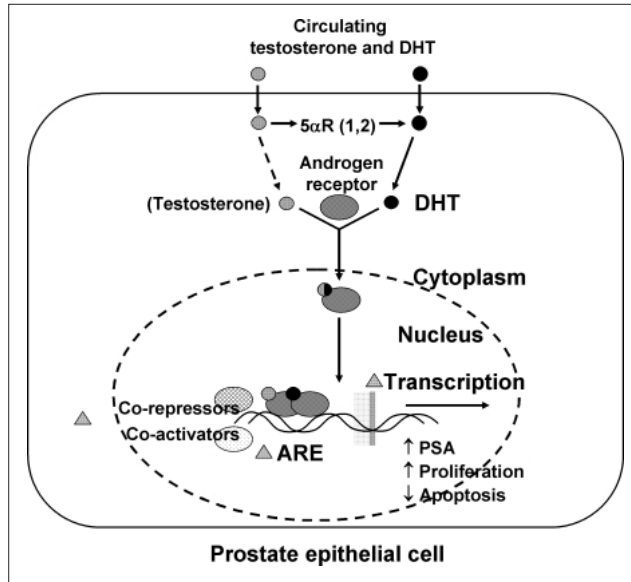
## Synergistic Influence of Combined Nutrients and Botanicals

Many researchers report the significant benefits of botanicals for addressing BPH and its adjunct issues. They often find increased effectiveness and benefits from combining herbal and/or nutrient compounds together. Botanicals have been used in this manner for many years in modern Europe, where herbal medicines are routinely dispensed for BPH with numerous human studies and clinical trials supporting this use. In Italy, almost half the medications given for BPH are herbal. Germany and Austria use herbal therapy as a first line of treatment for mild-to-moderate genito-urinary symptoms and herbal medicine accounts for about 90% of medications prescribed for BPH treatment.<sup>4</sup>

Multiple studies show strong evidence for the efficacy of Saw Palmetto and other herbs. Some studies find Saw Palmetto combined with Selenium and Lycopene to be more effective than Saw Palmetto alone to reduce prostate inflammation, epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), and oxidative stress along with prostate hyperplasia; offering significant relief from symptoms in those with chronic prostate conditions.<sup>4</sup>

The combination of Nettle Root and Pygeum showed significant improvement in urinary symptoms and decrease of overall symptoms in a study with 134 BPH subjects. The results were attributed to inhibition of the enzymes 5-alpha-reductase and aromatase. While Pygeum is recognized to significantly inhibit these enzymes and Nettle shows a weaker ability to inhibit these pathways, the combination was considered more effective than either alone.<sup>1</sup>

A study with 543 people over 48 weeks who took a combination of Saw Palmetto and Nettle Root for early stages of BPH found significant results in the decrease of symptoms and the increase of urinary flow.<sup>1</sup> Other studies find that combining botanicals such as Nettle Root and Pygeum with



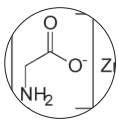
Source: [https://openi.nlm.nih.gov/detailedresult.php?img=PMC2440415\\_ijcp0062-1076-f1&req=4](https://openi.nlm.nih.gov/detailedresult.php?img=PMC2440415_ijcp0062-1076-f1&req=4)

Saw Palmetto increases the benefits, including a significant decrease in nocturia.<sup>5</sup>

An animal study reports a combination of Saw Palmetto, Selenium and Lycopene to be more effective than Saw Palmetto alone. Together they show increased anti-inflammatory activity and greatly reduced VEGF and EGF expression.<sup>6</sup> This combination is found to be more effective than Saw Palmetto alone to reduce prostate hyperplasia and

weight, promote apoptosis, and suppress EGF and VEGF in hyperplastic prostates.<sup>3</sup> A paper that reviewed some of the major and most recent findings on the therapeutic properties of three widely used compounds – Saw Palmetto, Lycopene, and Selenium – concluded that all three inhibit prostate cancer through the dual activity of inhibiting proliferation and inflammation within the prostate gland.<sup>7</sup>

## Botanicals and Nutrients to Decrease BPH Symptoms and Optimize Prostate Health



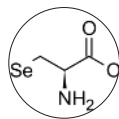
### Zinc Glycinate Chelate

The mineral Zinc is essential for growth and reproduction in humans. Necessary to maintain the structural integrity of DNA, Zinc is integral in the synthesis of nucleic acid and protein. It also plays a role in cellular metabolism, immune function, and wound healing, and is essential for the activity of over 100 enzymes. Zinc acts as a messenger in signal transduction.<sup>8-10</sup>

Zinc plays a vital role in the nuclear binding of androgen receptors in the formation of hormone receptor proteins. It also influences steroid synthesis and the metabolism of nutrients.<sup>10</sup> The prostate contains the highest concentration of Zinc of any soft tissue. High amounts of Zinc are secreted in the prostatic fluid.

Studies find that Zinc concentrations in malignant prostate

tissues are about 10% to 25% of those in normal prostate tissue. This suggests that Zinc homeostasis in the prostate is essential to prostate health, though the exact mechanisms are unclear. One theory proposes that dysregulation of Zinc transporters in the prostate can lead to disruption of Zinc homeostasis and contribute to formation of malignancies. Often low intracellular Zinc is found in human prostate cancer tissues or in prostate epithelial cancer cell lines.<sup>11</sup>



### Selenium Amino Acid Chelate

Selenium, an essential trace mineral, is found in Brazil nuts, whole grains, fish, and sunflower seeds as selenomethionine, which is a Selenium analog of methionine that exerts antioxidant and anti-inflammatory influence. Selenium comprises a key component of selenoproteins such as glutathione peroxidase. As such, it exerts antioxidant properties and helps prevent formation of

free radicals. Since it reduces reactive oxygen metabolites, glutathione peroxidase helps maintain cell membrane integrity by preventing oxidative damage to lipids, lipoproteins, and DNA.<sup>3,4;12-16</sup>

Selenium inhibits lipid peroxidation and is found to decrease the binding of various chemical compounds to DNA. Over 25 selenoproteins are known to exist in human biochemistry throughout the body. As a cofactor in various metabolic pathways, Selenium can act to modulate cell signal transduction.<sup>12-16</sup> Some studies suggest that Selenium supplementation can slow prostate growth through its ability to inhibit cell proliferation and to stimulate apoptosis.<sup>4</sup>



### Saw Palmetto (*Serenoa repens*)

Considered by Eclectic Physicians as a nutritive tonic, Saw Palmetto berries were used by Native Americans in the 18th century for testicular atrophy, erectile dysfunction, prostate gland swelling, as an aphrodisiac, and to improve sexual vigor. It was also traditionally used for urogenital tract infections.

Saw Palmetto berry contains fatty acids, plant sterols (including B-sitosterol), polysaccharides, flavonoids, carotenoids, and volatile oils. The plant sterols and fatty acids of Saw Palmetto berry are found to inhibit the 5-alpha-reductase enzyme that blocks the conversion of testosterone to di-hydro testosterone (DHT), which promotes prostate gland growth.

Saw Palmetto is thought to benefit prostate health through multiple mechanisms of action. It is found to block the activity of estrogen receptors in the prostate. It is a potent anti-inflammatory, exerts anti-proliferative influence, and stimulates apoptosis in prostate cells. Saw Palmetto influences the decrease of sex-hormone binding globulin (SHBG) and is found to inhibit proliferation of prostate cells induced by prolactin and growth-factors. It is also found to help reduce spasm of the bladder muscle.<sup>1,2,4,17-21</sup>

Saw Palmetto is considered the most widely used botanical for BPH. In numerous studies, compared with placebo, Saw Palmetto significantly improved urinary tract symptoms and flow, decreased nocturia, and alleviated BPH symptoms. Several studies also reported effective reduction of prostate size with administration of Saw Palmetto in addition to significant alleviation of BPH and urinary symptoms.<sup>1,4,17-20</sup> Improvement of symptoms was found comparable to those with the drug finasteride but without side effects.<sup>4,5</sup>

Various concentrations of Saw Palmetto were analyzed for cytotoxic effects on prostate cell lines and generic cancer cells. The extract inhibited proliferation of prostate-derived cell lines in a dose-dependent fashion. The berry extract reduces COX-2 expression, which is associated with an increased

incidence of prostate cancer.<sup>18</sup>



### Nettle (*Urtica dioica*)

In medieval times, Nettle root was valued as a diuretic and to alleviate joint problems. Studies find it beneficial for BPH and it is widely used for this condition, especially in Europe. Nettle root is used in Germany as a component of approved medicines for treatment of BPH.<sup>22</sup> Nettle root is approved by the German Commission E for treatment of urinary difficulty in BPH stages I and II. In a 6-month, double-blind placebo-controlled study, significant reduction in urinary tract symptoms was observed in those taking Nettle extract.<sup>23</sup> Nettle root contains plant sterols (including B-sitosterol), glycosides, glycoproteins, acids (including malic, salicylic and others), polysaccharides, fatty acids, and lignans.<sup>4</sup>

Nettle root extract is shown to exert potent anti-inflammatory influence. Compounds in Nettle root exert some influence to inhibit cell proliferation through modulation of hormonal binding to receptors on human prostatic membranes. Nettle extract is found to increase androgen binding capacity and to modulate SHBG binding to receptors on human prostatic membranes, which inhibits cellular growth within the prostate.<sup>1,24,25</sup>

Nettle extract is found to act on aromatase, EGF, and prostate steroid membrane receptors.<sup>26</sup> Specifically, the lignans of Nettle root inhibit sex hormone activity and block the binding of EGF. Nettle root is also found to inhibit proteolytic enzymes that are involved with genito-urinary inflammation and infections. Studies report that Nettle root is effective in decreasing the symptoms of BPH, and in some cases is found to help decrease prostate size. Researchers often find Nettle root is most effective when combined with Saw Palmetto and Pygeum.<sup>4</sup>



### Crateva nurvala

Crateva is a tree often found growing along the banks of rivers in the sub-Himalayan regions of India. The stem bark is valued in traditional Ayurvedic medicine as a kidney and urinary bladder tonic and is the preferred treatment for urinary disorders that reoccur. Crateva bark has the ability to increase the tone of smooth muscle. It is also used in the treatment of prostate enlargement especially with bladder sensitivity.<sup>27,28</sup>

In a human study, baseline measures of urinary function and bladder tone were assessed. With three months of ingestion of Crateva tea, significant improvement was found compared to baseline with an increase in healthy urinary function and bladder tone in these individuals.<sup>29</sup> Lupeol, a pentacyclic triterpene isolate of Crateva bark, is shown to exert anti-inflammatory activity along many pathways including NFkB (nuclear factor kappa-B).<sup>31</sup>

## Pumpkin Seed Oil (*Cucurbita pepo*)



Pumpkin seeds are valued worldwide as a nutritive food and powerful medicine. The Cherokee and Iroquois people valued pumpkin seeds as a pediatric urinary tonic and as a diuretic. Pumpkin seed is a folk remedy in Europe for bladder irritation and urinary disorders due to prostate issues.<sup>32</sup>

The German Commission E documents the usefulness of Pumpkin seed oil for supporting healthy prostate function. It is considered effective for stage I and II BPH, particularly for urinary symptoms including nocturia and incomplete emptying. The German Commission E also recognizes Pumpkin seeds as beneficial for irritable bladder.<sup>32</sup>

Pumpkin seeds contain ample amounts of plant sterols (including sitosterol, stigmasterol and others), fatty acids (rich in linoleic and oleic acids) and zinc. They also contain carotenoids (including lutein and B-carotene), tocopherols, and other compounds.<sup>1,4,32</sup>

The plant sterols found in Pumpkin seeds are found to significantly decrease elevated levels of DHT in humans with BPH. It is thought that Pumpkin seed phytosterols can bind to androgen receptors to help prevent prostate growth. Patients with mild BPH symptoms were given Pumpkin seed oil for three months with improvement in all parameters. Pumpkin seed is found to exert a tonic influence on the urinary bladder and to enhance relaxation of the sphincter at the neck of the bladder.<sup>1,4</sup>

## Pygeum (*Pygeum africanum*)



Pygeum is a tall evergreen tree native to Africa. The bark is found to be rich in phytosterols including B-sitosterol, B-sitosteryl glucoside, and B-sitostenone, and other sterols and steroid intermediates. It also contains triterpenoid acids and fatty acids. Pygeum bark has been used as a tea by Africans specifically for urinary disorders.<sup>4</sup>

Pygeum is found to be a potent inhibitor of oxidative damage within the prostate and also contains compounds that enhance prostate health. It is found to help reduce nocturia and relieve many of the genito-urinary symptoms of BPH.<sup>33-36</sup> It is thought to be effective through its anti-inflammatory actions and ability to inhibit numerous pathways that promote growth of the prostate gland. It is shown to exert protective influence on the urinary bladder and to exert antioxidant benefits.

In a number of controlled clinical trials with 1562 men, Pygeum demonstrated significant improvement in urologic parameters where nocturia was reduced by 19% and peak urine flow was increased by 23%.<sup>4</sup> Used in France to treat mild to moderate BPH since 1969, Pygeum is found to help calm prostate gland

inflammation and to alleviate nocturia, dysuria, and bladder fullness.<sup>1</sup>

Constituents in Pygeum include long-chain fatty alcohols, B-sitosterol, and other fatty acids. It contains trans-ferulic acid esters that are found to reduce cholesterol concentration in the prostate, which limits the synthesis of testosterone. Phytosterols, such as B-sitosterol, B-sitosterone, and campesterol, are found to compete with the precursors of androgens and to inhibit synthesis of prostaglandins. Triterpenes are found to exert anti-inflammatory influence in prostate connective tissue.<sup>1</sup>

## Lycopene



Lycopene, a member of the carotenoid family, is a natural fat-soluble pigment found in many fruits and vegetables, and is especially abundant in tomatoes. It is also found in watermelon, papaya, and pink grapefruit. Lycopene is shown to have an affinity for the prostate where it is found to concentrate in the prostate tissue. Lycopene exerts strong antioxidant activity and is found to inhibit cell growth in normal prostatic epithelial cells. It is reported to promote apoptosis in hyperplastic prostate tissue and to modulate cell-signaling. Lycopene is also found to inhibit 5-alpha-reductase (reducing production of DHT) and interleukin-6 signaling.<sup>4,37-39</sup> Human studies show that Lycopene helps improve prostate tissue health and decrease enlargement.<sup>40</sup>

## Black Pepper (*Piper nigrum*)



Black Pepper is widely known for its ability to enhance the bioavailability of herbs and nutrients. In Chinese and Ayurvedic medicine it is added to formulas for its ability to “move” other compounds to carry them throughout the body.

One way that piperine is thought to enhance bioavailability is through influencing the cellular biomembrane and intestinal enzymes.<sup>41-43</sup> Piperine is found to reduce levels of pro-inflammatory mediators including COX-2, IL factors, and TNF-alpha. It also supports healthy glutathione and superoxide dismutase levels.<sup>44,45</sup> It is found to inhibit VEGF and to modulate cytokine and growth factor responses.<sup>46</sup> Piperine is known to be antioxidative, antimutagenic, antibacterial, and hepato-protective.<sup>42,47</sup>

*For more information on any of the ingredients listed here, including extensive research or individual monographs compiled by Donnie Yance, please email [info@naturaedu.com](mailto:info@naturaedu.com).*

## References

1. Dvorkin L, Song KY. *Herbs for benign prostatic hyperplasia*. Ann Pharmacother. 2002 September. 36:1443-1452.
2. Comhaire F, Mahmoud A. *Preventing diseases of the prostate in the elderly using hormones and nutraceuticals*. Aging Male. 2004 June. 7(2):155-169.
3. Minutoli L, Bitto A, et al. *Serenoa Repens, lycopene and selenium: a triple therapeutic approach to manage benign prostatic hyperplasia*. Curr Med Chem. 2013. 20(10):1306-1312.
4. Pagano E, Laudato M, et al. *Phytotherapy of benign prostatic hyperplasia*. A minireview. Phytother Res. 2014. 28:949-955. DOI: 10.1002/ptr.5084
5. Wilt TJ, Ishani A, et al. *Phytotherapy for benign prostatic hyperplasia*. Public Health Nutr. 2000 Dec. 3(4A):459-72.
6. Altavilla D, Bitto A, et al. *The combination of Serenoa repens, selenium and lycopene is more effective than serenoa repens alone to prevent hormone dependent prostatic growth*. J Urol. 2011 Oct. 186(4):1524-1529. doi: 10.1016/j.juro.2011.05.049. Epub 2011 Aug 19.
7. Gerber GS. *Saw palmetto for the treatment of men with lower urinary tract symptoms*. J Urol. 2000 May. 163(5):1408-12.
8. Web: <https://ods.od.nih.gov/factsheets/Zinc-HealthProfessional/>
9. Haase H, Rink L. *Multiple impacts of zinc on immune function*. Metallomics. 2014 Feb 17.
10. Om AS, Chung KW. *Dietary zinc deficiency alters 5a-reduction and aromatization of testosterone and androgen and estrogen receptors in rat liver*. J Nutr. 1996 January. 842-848.
11. Song Y, Elias V. *Marginal zinc deficiency increases oxidative DNA damage in the prostate after chronic exercise*. Free Radical Biology & Medicine. 2010. 48:82-88.
12. Patterson BH, Levander OA. *Naturally occurring selenium compounds in cancer chemoprevention trials: A workshop summary*. Cancer Epidemiol Biomarkers Prev. 1997. 6:63-69.
13. Fleet JC. *Dietary selenium repletion may reduce cancer incidence in people at high risk who live in areas with low soil selenium*. Nutr Rev 1997. 55:277-9.
14. Soriano-Garcia M. *Organoselenium compounds as potential therapeutic and chemopreventive agents: a review*. Curr Med Chem. 2004 Jun. 11(12):1657-69.
15. Patrick L. *Selenium Biochemistry and Cancer: A Review of the Literature*. Alt Med Rev. 2004. (9)3:239-258.
16. *Selenium Monograph*. Alt Med Review. 2003. (8)1: 63-71.
17. Gerber GS, Kuznetsov D, et al. *Randomized, double-blind, placebo-controlled trial of saw palmetto in men with lower urinary tract symptoms*. Urology. 2001Dec. 58(6):960-4; discussion 964-5,
18. Goldmann, Dr. W.H. *Saw Palmetto Berry Extract Inhibits Prostate Cancer Cell Growth In Vitro*. Children's Hospital in Boston Dec. 13, 2001.
19. Vela Navarrete R, Garcia Cardoso JV, et al. *BPH and inflammation: pharmacological effects of Permixon on histological and molecular inflammatory markers*. Results of a double blind pilot clinical assay. Eur Urol. 2003 Nov. 44(5):549-55.
20. Giannakopoulos X, Baltogiannis D, et al. *The lipidosterolic extract of Serenoa repens in the treatment of benign prostatic hyperplasia: a comparison of two dosage regimens*. Adv Ther. 2002 Nov-Dec.19(6):285-96.
21. Hostanska K, Suter A, et al. *Evaluation of cell death caused by an ethanolic extract of Serenoa repens fructus (Prostasan) on human carcinoma cell lines*. Anticancer Res. 2007 Mar-Apr. 27(2):873-81.
22. *Nettle Root. Herbal Medicine: Expanded Commission E Monographs*. American Botanical Council. 2000.
23. Safarinejad MR. *Urtica dioica for treatment of benign prostatic hyperplasia: a prospective, randomized, double-blind, placebo-controlled, crossover study*. J Herb Pharmacother. 2005. 5(4):1-11.
24. Schneider T, Rubben H. *Stinging nettle root extract (Bazoton-uno) in long term treatment of benign prostatic syndrome (BPS). Results of a randomized, double-blind, placebo controlled multicenter study after 12 months*. Urologe A. 2004 Mar. 43(3):302-306.
25. Hryb DJ, Khan MS, et al. *The effect of extracts of the roots of the stinging nettle (Urtica dioica) on the interaction of SHBG with its receptor on human prostatic membranes*. Planta Med. 1995 Feb. 61(1):31-32.
26. Chrubasik JE, Roufogalis BD, et al. *A comprehensive review on the stinging nettle effect and efficacy profiles. Part II: urticae radix*. Phytomedicine. 2007 Aug. 14(7-8):568-579. Epub 2007 May 16.
27. Varalakshmi P, et al. *Effect of Crateva nurvala on the Biochemistry of the Small Intestinal Tract of Normal and Stone-forming Rats*. J Ethnopharmacology. 1991. 31:67-73.
28. Deshpande PJ, et al. *Crateva nurvala Hook and Forst (Varuna)- the Ayurvedic drug of choice in urinary disorders*. Indian J Med Res. 1982. 76 (Suppl): 46-53.
29. Kumar P, Singh LM, Deshpande PJ. *Clinical study with Crataeva nurvala in urinary tract infection*. J Scient Res in Plant Medicine. 1982. (3)2/3:75-79.
30. Bopana N, Saxena S. *Crataeva nurvala: A Valuable Medicinal Plant*. J Herbs, Spices & Medicinal Plants. 2008 September. (14)1/2:107-112.
31. Saleem M. *Lupeol, a novel anti-inflammatory and anti-cancer dietary triterpene*. Cancer Letters. 2009. 285:109-115.
32. *Pumpkin Seed. Herbal Medicine: Expanded Commission E Monographs*. American Botanical Council. 2000.

## Pygeum

33. Doufour B, et al. *Etude controlee des effets de l'extrait de Pygeum africanum sur les symptomes fonctionnelles de l'adenome prostatique*. Ann. Urol. 1984. (18):193-195.
34. Riffaud MC, Riffaud JP. *Pygeum africanum extract for the treatment of patients with benign prostatic hyperplasia: a review of 25 years of published experience*. Current Therapeutic Research 1995. 56(8):796-817.
35. Ishani A, MacDonald R, et al. *Pygeum africanum for the treatment of patients with benign prostatic hyperplasia: a systematic review and quantitative meta-analysis*. Am J Med. 2000. 109(8):654-664.
36. Chatelain C, Autet W, Brackman F. *Comparison of once and twice daily dosage forms of Pygeum africanum extract in patients with benign prostatic hyperplasia: a randomized, double-blind study, with long-term open label extension*. Urology. 1999. 54(3):473-478.

## Lycopene

37. Agarwal D, Rao AV. *Tomato lycopene and its role in human health and chronic diseases*. CMAJ. 2000. 163:739-744.
38. Sharoni Y, Danilenko M, Levy J. *Molecular mechanisms for the anticancer activity of the carotenoid lycopene*. Drug Dev Res. 2000. 50:448-456.
39. Patton D. *Lycopene, the carotenoid found in tomatoes, may reduce the risk of prostate cancer by inhibiting the male hormone's effect on the prostate*. 2004. online edition of FASEB (doi:10.1096/fj.03-1116fje) 15/04/2004
40. Schwarz S, Obermüller-Jevic UC, et al. *Lycopene inhibits disease progression in patients with benign prostate hyperplasia*. J Nutr. 2008 Jan. 138(1):49-53.

## Black Pepper

41. Patil, UK, Singh A, et al. *Role of Piperine As A Bioavailability Enhancer*. International Journal of Recent Advances in Pharmaceutical Research. October 2011. 4:16-23.
42. Ahmad N, Fazal H et al. *Biological role of Piper nigrum L. (Black pepper): A review*. Asian Pacific Journal of Tropical Biomedicine. 2012. S1945-S1953.
43. Vasavirama K, Upender M. K. *Piperine: A valuable alkaloid from Piper species*. Int J Pharm Pharm Sci. Vol 6(4): 34-38.
44. Umar S, Golam Sarwar AH, Umar K, et al. *Piperine ameliorates oxidative stress, inflammation and histological outcome in collagen induced arthritis*. Cell Immunol. 2013 Jul 19. 284(1-2):51-59. doi: 10.1016/j.cellimm.2013.07.004.
45. Ying X, Chen X, Cheng S, et al. *Piperine inhibits IL- $\alpha$  induced expression of inflammatory mediators in human osteoarthritis chondrocyte*. Int Immunopharmacol. 2013 Oct. 17(2):293-299. doi: 10.1016/j.intimp.2013.06.025. Epub 2013 Jul 6.
46. Sunila ES, Kuttan G. *Piper longum inhibits VEGF and proinflammatory cytokines and tumor-induced angiogenesis in C57BL/6 mice*. International Immunopharmacology. 2006. 6:733- 741.
47. Matsuda H, Ninomiya K, et al. *Hepatoprotective amide constituents from the fruit of Piper chaba: Structural requirements, mode of action, and new amides*. Bioorg Med Chem. 2009 Oct 15. 17(20):7313-23. Epub 2009 Aug 29.