Fatty Acids in Some Cooking Oils as Agents of Hormonal Manipulation in a Rat Model of Benign Prostate Cancer

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Summary: Anti-androgenic substances, mainly prostate 5\alpha-reductase inhibitors, used in the treatment of benign prostatic hyperplasia (BPH) have been associated with side effects in man and animals. To reduce these side effects as well as suppress BPH development, the management of the condition has come to include dietary interventions. This study investigated the effect of some cooking oils on testosterone-induced hyperplasia of the prostate in rats. Male Sprague-dawley rats were distributed into eighteen groups (n=6) as A-R. A negative control group was injected subcutaneously with soya oil; while prostatic hyperplasia was induced subcutaneously in groups B-R with 3mg/kg testosterone daily for 14 days. Group B was the positive control (BPH group) while groups C-R were also administered orally 800mg/kg of coconut, castor, canola, cottonseed, pomegranate, blackseed, sheabutter, olive oil, codliver, sardine, palm, repeatedly heated palm (RHPO), vegetable, repeatedly-heated vegetable (RHVO), sesame, and groundnut oils respectively, daily, for 14 days. Blood sample was drawn via retro-orbital sinus for the estimation of serum testosterone(T) and dihydrotestosterone (DHT) level and rats were thereafter euthanized to obtain the prostates for T and DHT determination as well as tissue weights. Data are mean ± SEM, compared by ANOVA. The oils significantly reduced the increase in prostate weight (PW) to body weight (BW) ratio to body weight (BW) ratio induced by testosterone. Apart from the fact that all the oils reduced the PW:BW ratio, the blackseed, sheabutter, sardine, vegetable and groundnut oils suppressed the DHT level in the serum, while pomegranate, olive, RHPO reduced DHT level in the prostate compared to the BPH rats. This study suggests that blackseed, sheabutter, sardine, vegetable, groundnut, pomegranate, olive, and RHPO oils could inhibit testosterone-induced hyperplasia of the prostate and therefore may be beneficial in the management of BPH.

Keywords: benign prostatic hyperplasia, cooking oils, fatty acids, rat, dihydrotestosterone, testosterone

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is an enlargement of the prostate gland from progressive hyperplasia or abnormal growth of cells of glandular epithelial and stromal cells. It is associated with impairment in urinary function, as such it is a common urogenital disorder that affects up to 85% of men over 50 years of age (Arruzazabala \textit{et al.}, 2007). The inability to delay urination, incomplete emptying of the bladder, bladder outlet obstruction, bloody urination, nocturia, as well as dysuria, are common symptoms of BPH (Barkin, 2011). Although BPH is not a known risk factor for prostate cancer, it may increase the chance of its occurrence (Chang \textit{et al.}, 2012).

The hormones, testosterone (T) and dihydrotestosterone (DHT) have key roles to play in the development and growth of the entire male genital tract, as such they stimulate differentiation of the prostate gland (Andriole \textit{et al.}, 2004). The adrenal glands and testes synthesize testosterone, and the enzyme prostatic 5\alpha-reductase type 2, converts it to DHT (Carson and Rittmaster, 2003). DHT then binds to the androgen receptor (AR), which is transported to the nucleus, where it regulates genes important for prostate growth and differentiation (Mizokami \textit{et al.}, 2009). When aging sets in, the production and accumulation of DHT in the prostate increases, thus encouraging cell growth and causing hyperplasia (Carson and Rittmaster, 2003, Arruzazabala \textit{et al.}, 2007). Risk factors such as race, ethnicity and family history of prostate cancer occurrence play important roles in the development of BPH. In addition, environmental factors like diet also play a role in prostate cancer incidence. The increase in prostate disorders because of dietary changes has been demonstrated in both human and animal studies (Rohrmann \textit{et al.}, 2007, Torricelli \textit{et al.}, 2013). Drugs, such as Finasteride® developed with a focus to
reducing DHT level in BPH patients have been associated with side effects such as nasal congestion, decreased libido, erectile dysfunction and so on. Thus, to reduce these side effects as well as suppress BPH development, the management of the condition has come to include dietary interventions as well as natural materials such nutraceutical preparations which include pumpkin seed oil (Gossell-Williams et al., 2006), coconut oil (Arruzazabala et al., 2007) as well as herbal extracts mainly saw palmetto lipid extracts (SPLC) (Arruzazabala et al., 2007).

Over the last few decades, there has been a growing public concern about the significant interplay between health, food and nutrition. Fat is an essential macronutrient of the human diet and vegetable oils represent a more highly consumed fat. The effects of high-fat diet mainly in fatty acids have been the emphasis of several dietary guidelines targeting the reduction of some diseases and especially cancer prevention. In this investigation, we employed a BPH model (testosterone propionate (TP)-induced BPH) to examine whether oral dosing with coconut, castor, canola, cottonseed, pomegranate seed, blackseed, sheabutter, olive, cod-liver, sardine, palm, repeatedly-heated palm, vegetable, repeatedly-heated vegetable, sesame and groundnut oils could prevent prostatic hyperplasia induced by testosterone in rats.

MATERIALS AND METHODS

Animals
Adult male Sprague-Dawley rats, 12 weeks old and weighing 350-370g, were obtained from the Animal house of the College of Medicine, University of Lagos and adapted to laboratory conditions (25 ± 3°C), relative humidity 61± 3%, light/dark cycles of (12 h) for 7 days. Free access to feed (rodent chow was from Centre Point Agro and Livestock Raw Materials Depot, Lagos) and water ad libitum were provided. Animal handling and experimental protocols were conducted in accordance with the NIH Guidelines for the Care and Use of Laboratory Animals.

Oils
Extra-virgin coconut oil (Andalucia, Spain ), castor oil (KTC Limited, UK ), canola oil (ConAgra Foods, USA), cottonseed oil (Shamad Concept, Nigeria), pomegranate oil (Hemani, Pakistan), blackseed oil (Hemani, Pakistan), sheabutter (bought in a market in Lagos, Nigeria), olive oil (ICEA, Bologna), codliver oil (Olive Healthcare, India), sardine (UNIMER, Morrocco), palm oil (Farmland produce, Nigeria), repeatedly-heated palm oil (palm oil was used for frying beef and plantain 3 consecutive times at 180°C), vegetable oil (Laziz vegetable oil, Apple & Pears Ltd. Nigeria), repeatedly-heated vegetable oil (vegetable oil was used for frying beef and plantain 3 consecutive times at 180°C), sesame oil (OPW Ingredients GmBH, Germany), groundnut oil (bought from a market in Nigeria), groundnut oil (bought from a market in Nigeria), groundnut oil (bought from a market in Nigeria).

Administration and dosage of oils
Testosterone propionate (Cuban Medical Pharmaceutical Industry, Cuba), was diluted in soya oil and injected subcutaneously at 3mg/kg, daily for 14 days as described previously (Arruzazabala et al., 2004; Noa et al., 2005). Oils were diluted in soya oil and administered orally at 800mg/kg as this dose showed better inhibition against BPH model in rats (Arruzazabala et al., 2007). The rats were randomly distributed into eighteen groups (6 rats each): the negative control (Group A), received daily subcutaneous injection of soya oil (vehicle) and seventeen groups received daily subcutaneous injection of testosterone at 3mg/kg dosage. Group B was the positive control (BPH) while the other sixteen groups received subcutaneous injection of testosterone propionate plus oral administration of 800mg/kg of the oils as follows: Group C: coconut oil, Group D: castor oil, Group E: canola oil, Group F: cottonseed oil, Group G: pomegranate seed oil, Group H: blackseed oil, Group I: sheabutter, Group J: olive oil, Group K: codliver oil, Group L: sardine oil, Group M: palm oil, Group N: repeatedly-heated palm oil (RHPO), Group O: vegetable oil, Group P: repeatedly-heated vegetable oil, Group Q: sesame oil, Group R: groundnut oil. The treatments were administered for 14 days.

Body and prostate weight
The animals were weighed at the start of the experiment, the day before administration of oils and weekly thereafter. At the end of the experiment, animals were euthanized with CO2 anaesthesia, and blood samples were collected and centrifuged at 5000 revs for 10 minutes while the prostates were carefully recovered and weighed using a digital weighing scale (Scout Pro, Ohaus Corporation, USA) immediately and frozen for further studies. The prostate weight (PW) and prostate weight to body weight ratios (PW/BW) were recorded. Percentage inhibition was calculated as follows: 100-[(TG-NC)/(PC-NC) x 100]. where PC, NC, and TG were the values of the positive control, negative control, and treated groups, respectively.

Measurement of DHT and T levels in the serum and prostate
Prostate tissue was homogenized in lysis buffer containing protease inhibitors (50 mM Tris–HCl [pH 7.4], 150 mM NaCl, 1 mM EDTA, 0.5% NP-40, 0.1% SDS, 1 mM EGTA, 100 μg/mL PMSF, 10 μg/mL pepstatin A, and 100 μM Na3VO3). The homogenates were centrifuged at 5000 revs for 10 mins at 4°C, and the protein concentrations in the supernatant fractions were determined using Bradford reagent (Bio-Rad, Hercules, CA). Enzyme-linked immunosorbent assays
(ELISAs) were performed according to the manufacturer’s instructions. DHT and testosterone levels in the serum and prostates were measured with ELISA kits (Sigma, USA).

Statistical Analysis
Data are expressed as mean ± standard error of mean (SEM) and were analyzed with Graphpad software version 3.05(San Diego, California, U.S.A.) using one-way ANOVA for multiple comparisons between groups, followed by the student-Newman-Keuls test, differences between groups were considered significant at P<0.0001.

RESULTS
Effect of cooking oils on prostate weight and PW/BW ratio
Table 1 summarizes the effects of the oils on testosterone -induced prostate enlargement. PW and PW/BW ratio increased in the positive control compared with negative control group. The cooking oils: coconut (C) , castor (D), canola (E), cottonseed (F), pomegranate (G), blackseed (H), sheabutter (I), olive (J), codliver (K), sardine (L), palm (M), RHPO (N) vegetable (O), RHVO (P), sesame (Q) and groundnut (R ) when compared with the positive control significantly decreased the PW gain induced with testosterone by 65.2%, 60.6%, 63.6%, 72.3%, 68.2%, 65.2%, 71.2%, 65.2%, 62.1%, 72.7%, 48.5%, 59.1%, 50.0%, 50.0%, 48.5%, 66.7% respectively. Although the percentage inhibition achieved with palm oil (M) and sesame (Q) were lower compared with those achieved by the other oils. The increase in PW/BW ratio which was as a result of the testosterone-induced prostate enlargement was also decreased by the oils as follows: coconut (C) 68.6% , castor (D) 54.9%, canola (E)52.5%, cottonseed (F)59.7%, pomegranate (G)60.41%, blackseed (H)53.93%, sheabutter (I)65.8%, olive (J)59.1%, codliver (K)56.3%, sardine (L)56.7%, palm (M)60.1%, RHPO (N)62.1%, vegetable (O)54.6%, RHVO (P)55.9%, sesame (Q)54.3% and groundnut (R ) 62.5%.

Effect of cooking oils on testosterone and DHT levels in the serum
Castor oil, and sheabutter induced a decrease in the testosterone serum level compared to the BPH (positive control) group, while the vegetable oil had an increased level compared to the BPH group. The vegetable, sardine, palm oil, RHVO, RHPO, coconut, canola, cottonseed, sesame, codliver, groundnut, blackseed, olive, pomegranate, sheabutter and castor oil levels were significantly increased compared with the negative control. Group D, the castor oil induced a significant decrease compared to vegetable, sardine, palm, RHVO, RHPO, coconut and canola oils while sheabutter group induced a significant decrease compared to the vegetable, sardine, palm, RHVO, RHPO, and coconut oils. The pomegranate seed oil also induced a significant decrease compared to the vegetable, sardine and palm oils; while olive oil induced a significant decrease compared to vegetable and sardine oils. Blackseed oil induced a significant decrease compared to the vegetable and sardine oils. Groundnut, codliver, cottonseed, canola, coconut, and RHPO oils all induced significant decreases compared to the vegetable oil. Sesame oil induced a significant decrease compared to the sardine oil (Fig 1).

<table>
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<th>Groups</th>
<th>PW (g)</th>
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<th>PW/BW (x10^{-3})</th>
<th>% inhibition</th>
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<td>-</td>
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<td>-</td>
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<tr>
<td>B</td>
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<td>-</td>
<td>4.33±0.05</td>
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<tr>
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</table>

PW, prostate weight; BW, body weight; Positive control (BPH), received administration of testosterone (s.c) injection Negative control= Group A, Positive control (BPH) = Group B, BPH +coconut oil= Group C, BPH + castor oil =Group D, BPH +canola oil = Group E, BPH +cottonseed oil = Group F, BPH +pomegranate seed oil = Group G, BPH +blackseed oil=Group H, BPH +shea butter = Group I, BPH +olive oil = Group J, BPH +cod liver oil =Group K, BPH + sardine oil =Group L, BPH + palm oil =Group M, BPH + RHPO = Group N, BPH +vegetable oil = Group O, BPH +RHVO = Group P, BPH +sesame oil = Group Q, BPH +groundnut oil= Group R.
Fig. 1 Effect of cooking oils on serum testosterone levels. Values are expressed as mean ± SEM, n=6/group. *P< 0.0001 vs BPH, #P< 0.0001 vs negative control, αP< 0.0001 vs C,E,L,M,N,O,P, βP< 0.0001 vs C,L,M,N,O,P, µP< 0.0001 vs L,M,O, γP< 0.0001 vs L, δP< 0.0001 vs O. Negative control= Group A, Positive control (BPH) = Group B, BPH +coconut oil = Group C, BPH + castor oil = Group D, BPH +canola oil = Group E, BPH +pomegranate seed oil = Group F, BPH +blackseed oil = Group G, BPH +blackseed oil=Group H, BPH +shea butter = Group I, BPH +olive oil = Group J, BPH +cod liver oil =Group K, BPH + sardine oil = Group L, BPH + palm oil =Group M, BPH + RHPO = Group N, BPH +vegetable oil = Group O, BPH +RHVO = Group P, BPH +sesame oil = Group Q, BPH +groundnut oil= Group R.

Fig 2 Effect of cooking oils on serum DHT levels. Values are expressed as mean ± SEM, n=6/group. *P< 0.0001 vs BPH, #P< 0.0001 vs D, E,J,M,N αP< 0.0001 vs E, βP< 0.0001 vs E. Negative control= Group A, Positive control (BPH) = Group B, BPH +coconut oil= Group C, BPH + castor oil =Group D, BPH +canola oil = Group E, BPH +pomegranate seed oil = Group F, BPH +blackseed oil = Group G, BPH +blackseed oil=Group H, BPH +shea butter = Group I, BPH +olive oil = Group J, BPH +cod liver oil =Group K, BPH + sardine oil = Group L, BPH + palm oil =Group M, BPH + RHPO = Group N, BPH +vegetable oil = Group O, BPH +RHVO = Group P, BPH +sesame oil = Group Q, BPH +groundnut oil= Group R.

The blackseed, sheabutter, sardine, vegetable and groundnut oils induced a significant decrease in the DHT serum level in the rats compared to the BPH group. The vegetable oil induced a significant decrease compared to the canola, olive, palm, castor, RHPO oils. Groundnut oil induced a significant decrease compared to canola, olive, palm, castor and RHPO oils. Sheabutter, blackseed, sardine, sesame and cottonseed oils induced significant decrease compared to canola and olive oils, while codliver oil induced a significant decrease compared to canola oil only.

Effect of cooking oils on testosterone and DHT levels in the prostate

The castor oil induced a significant decrease in the testosterone prostate homogenate level compared to the BPH group while palm, vegetable, RHVO, sesame, and groundnut oils had increased levels compared to the BPH group. The castor oil and codliver oil induced
significant decrease compared to palm, sesame, RHVO, groundnut, vegetable and sardine oils. Sheabutter, canola, RHPo, cottonseed, olive, coconut and blackseed oils induced significant decrease compared to palm, sesame, RHVO, groundnut and vegetable oils. Sardine, vegetable, groundnut, RHVO oils induced significant decrease compared to palm and sesame oils. Pomegranate seed oil induced a significant decrease compared to palm, sesame, RHVO, groundnut oils while sesame oil induced a significant decrease compared to palm oil only (Fig 3).

The pomegranate seed oil, olive oil, RHPO, induced significant decrease in the DHT prostate homogenate oil compared to the BPH group while palm and blackseed oils induced an increase compared to the BPH group. Differences within the groups are as follows: Olive oil induced a significant decrease compared to palm, blackseed, sesame, sardine, canola, groundnut, vegetable, coconut, cod liver, sheabutter, cottonseed, and castor oils. RHPO induced a significant decrease compared to palm, blackseed, sesame, sardine, canola, groundnut, vegetable and coconut oils. RHVO and pomegranate oils induced significant decrease compared to palm, blackseed, sesame, and sardine oils. Castor, cottonseed, sheabutter and cod liver oils induced significant decrease compared to palm and blackseed oils. Coconut, vegetable, groundnut, canola, sardine, sesame and blackseed oils induced significant decrease compared to palm oil.

**DISCUSSION**

This study revealed that the oils administered orally at 800mg/kg for 14days significantly inhibited the increased prostate weight (PW) and the prostate to body weight (PW/BW) ratio induced by testosterone in the rats. Studies have shown that PW gain induced by testosterone in rats is accompanied by histological changes indicative of prostatic hyperplasia (PH), and that treatments that prevented the increase in PW also lowered histological scores of PH (Mitra et al., 1999, Noa et al., 2005). Thus, the effects of these oils on PW increase and increase in PW/BW can be explained as preventive effects on testosterone -induced PH in rats. The inhibitory effect of coconut oil on PW (65.2%), and PW/BW ratio (68.6%) found in this study is consistent with the report of Arruzazabala et al., (2007) who stated that a significant inhibition in the increase in PW (82.0%) and PW/BW ratio (74.3%) respectively also at a dose of 800mg/kg administered orally for 14 days was achieved. The effects of coconut oil are consistent with its high lauric and myristic acids. It is worthy to note that the oils used in this study contains oleic, linoleic, myristic or lauric acids and at varying appreciable concentrations, these fatty acids had been documented to inhibit 5α-reductase enzyme which converts testosterone into dihydrotestosterone thus their preventive effects (Gossell-Williams et al., 2006, Raynaud et al., 2002, Tsai et al., 2006).

Lauric and oleic acids have been discovered to inhibit the activity of both 5α-reductase isofoms. Several substances that have been implicated to inhibit BPH have fatty acid components. Saw palmetto lipid extracts (SPLLE) have been shown to possess lauric, oleic and myristic acids (Arruzazabala et al., 2011). D-004, a lipid extract of royal palm (Rostonymea regia) fruit has been shown to contain a mixture of free fatty acids, and oleic, lauric, palmitic and myristic acids were its major components (Arruzazabala et al., 2011).

The presence of excess polar compounds in repeatedly heated frying oil has been associated with increased risk of developing hypertension (Azman et al., 2012). This is because the consumption of repeatedly used frying oil might increase the risk of developing atherosclerosis (Williams et al., 1999). The consumption of repeatedly-heated cooking oil has also been associated with increased total serum and low-density lipoprotein (LDL) level. In another study, repeatedly heated oil increased lipid peroxidation and LDL in ovariectomized female rats suggesting that repeatedly- heated oil may contribute to the pathogenesis of atherosclerosis in post-menopausal women (Siti et al., 2008). The fatty acid components present in the palm oil were also present in the RHPO. Even though it was re-heated three times. Palm oil contains a high percentage of oleic and a little linoleic acid. In this study however, both repeatedly-heated palm and vegetable oils ameliorated the effect of BPH in the rats. This is because of the presence of oleic and linoleic acids in the oils and these acids have been shown to reduce the activity of BPH. Pomegranate seed oil also contains a little percentage of oleic acid and linoleic acid but a large percentage of punicic acid (PA) which has been implicated to possess anticancer attributes. In a study PA inhibited breast cancer cell proliferation through its lipid properties and by affecting the protein kinase C pathway (Grossmann et al., 2010). PA has also been found to inhibit both proliferation of cell lines and secretion of proinflammatory cytokines (Rocha et al., 2012). PA decreased tumour activity in mice skin cancer cells (Hora et al., 2003). Anticancer effects of PA have also been studied in prostate cancers. PA inhibits the expression of prostate specific antigen and steroid 5α-reductase type and dihydrotestosterone-induced androgen receptor nuclear accumulation. Studies also showed that PA stimulated DNA fragmentation and internal apoptotic activity through caspase-dependent pathway (Gasmi and Sanderson, 2010). This study has been able to relate with the recently renewed drive to identify natural remedies such as pomegranate plant to fight prostate cancer (Wang and Martins-Green, 2014).

Androgenic hormones, testosterone (T) and dihydrotestosterone (DHT) play crucial roles in the aetiology of BPH (Carson and Rittmaster, 2003). BPH
is caused by DHT, a metabolite obtained from the conversion of T by 5α-reductase (Mc Connell et al., 1992). Subsequently, inhibitors of 5α-reductase which block production of DHT ultimately slow down the development of BPH. The two main classes of drugs used as BPH treatments are inhibitors of α1-adrenoceptor inhibitors, which inhibit smooth muscle cell contraction (Furuya et al., 1982), and inhibitors of type II 5α-reductase, an enzyme responsible for the conversion of testosterone to the more potent androgen dihydrotestosterone (DHT) (Griffiths and Denis, 2000). Steroid 5α-reductase converts testosterone to DHT, an active form of androgen, in the prostate. Increased production of DHT results in the development of prostatic hyperplasia (Pais, 2010). DHT has 10 times higher affinity for the androgen receptor than testosterone as such DHT easily binds to androgen receptor, which stimulates the transcription of growth factors that are mitogenic for the epithelial and stromal cells for prostate (Carson and Rittmaster, 2003). The importance of DHT in prostatic hyperplasia was demonstrated by previous studies in which an inhibitor of 5α-reductase was administered to experimental animals with BPH (Roehrborn, 2011). These findings agree with our results. In this study, blackseed, sheabutter, sardine, vegetable and groundnut oils reduced the DHT level in the serum, while pomegranate, olive, RHPO reduced the DHT level in the prostate compared to the BPH rats. These results thus suggest that blackseed, sheabutter, sardine, vegetable, groundnut, pomegranate, olive, and RHPO oils inhibited the development of BPH via downregulation of DHT.

The testosterone serum level in the castor oil and sheabutter groups were decreased compared to the BPH group while the castor oil group also had a decreased prostate testosterone level compared to the BPH group. The palm, vegetable, RHVO, sesame, and groundnut groups had the testosterone prostate levels increased compared to BPH group while the vegetable oil group increased the testosterone level compared to the BPH group. To the best of our knowledge, no study on fatty acid based dietary intervention or natural materials such as pumpkin seed oil (Gossell-Williams et al., 2006), coconut oil (Arruzazabala et al., 2007) as well as herbal extracts mainly saw palmetto lipid extracts (SPLC) (Arruzazabala et al., 2007) have investigated the effect of DHT and T levels of such substances in experimental BPH, although some studies have shown an increase in T level of some drugs like Finasteride®. According to Pais, (2010) and Roehrborn, (2011), the administration of Finasteride® showed that the testosterone level was increased compared with that of BPH animals and in these studies, it was due to the inhibition of the transformation of testosterone to DHT. Unlike Finasteride®, sheabutter significantly reduced the concentrations of both testosterone and DHT compared with the BPH treatment group. It is suggested that the inhibitory effect of sheabutter likely occurs at the time of the development of BPH (Park 2016).

In this study the pomegranate seed oil significantly reduced the testosterone-induced prostate enlargement as well as the increase in PW and PW/BW ratios by 68.2%; 60.4% respectively as well as reducing the DHT prostate level. The anticarcinogenic properties of pomegranate seed oil could be because of its anticarcinogenic activities and inhibition of prostaglandin synthesis. Dietary pomegranate seed oil has been observed to diminish the growth of human prostate cancer LNCaP and DU145 cells to significantly reduce the invasiveness of the PC-3 cell line (Albrecht et al., 2004). The anticancer activity of punicic acid (PA) is mediated by decreasing cell migration and CXCL12 chemotaxis, increasing cell adhesion as well as inhibiting epithelial-mesenchymal transition and inhibiting angiogenesis and proliferation (Wang et al., 2012). The antitemstatic effect of PA occur via targeting hyaluronan signalling pathways in prostate cancer cells, in addition, PA possibly inhibits cytokine and chemokine pathways as well (Wang et al., 2011).

Blackseed, shea butter, sardine, vegetable, groundnut, pomegranate, olive, and RHPO oils administered orally at 800mg/kg appeared to be effective in reducing established prostate hyperplasia.

REFERENCES


