Review: Anti-Oxidant and Anti-Aging Properties of Equol in Prostate Health (BPH)

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ABSTRACT
Benign prostatic hyperplasia (BPH) is the pathological cellular progression of glandular proliferation associated with aging. The primary changes in prostate disorders are mediated by the conversion of the principle androgen, testosterone, to its more potent metabolite, 5α-dihydrotestosterone (5α-DHT). However, recent evidence suggests that estrogen hormonal actions via estrogen receptor subtypes also play an important role in BPH. Current pharmaceutical options for BPH have advantages, limitations and adverse effects. Complementary and Alternative Medicine (CAM) treatments for BPH include botanicals such as polyphenols and isoflavones. Equol is a polyphenolic/isoflavonoid molecule derived from intestinal metabolism, dairy and dietary plant sources. Equol has potent anti-oxidant and anti-aging properties to decrease prostatic irritation and potentially neoplastic growth. It has the unique characteristic to bind specifically 5α-DHT by sequestering 5α-DHT from the androgen receptor (AR), thus decreasing androgen hormone actions to improve prostate health by acting as a selective androgen modulator (SAM). It also has affinity for estrogen related receptor gamma (ERR-γ) and estrogen receptor beta (ER-β) within the prostate that is known to improve male health via selective estrogen receptor modulatory (SERM) activities to decrease inflammation, cellular proliferation and carcinogenesis. The possible clinical efficacy of equol on the symptoms associated with BPH is presented and the reviewed findings suggest that equol may provide a well-tolerated and rapid beneficial therapy for BPH that can be used alone or in combination with current pharmaceutical therapies. The beneficial clinical efficacy of equol observed may be due to the multiple positive biological actions that are not present in current pharmaceutical treatments.

KEYWORDS
Androgens; Estrogens; Isoflavonoid; Equol; BPH; SERM; Selective Androgen Modulator (SAM)

1. Introduction
Benign prostatic hyperplasia (BPH) is the pathological progression of epithelial and stromal proliferation in the prostate gland and the most common benign neoplasm in American men [1]. These changes are mediated primarily by 5α-dihydrotestosterone (5α-DHT) levels within the prostate [1,2] but estrogen hormonal actions via estrogen related receptor (ERR) gamma (γ) and estrogen receptor (ER) subtypes presumably play roles in BPH status [3,4]. There appears to be a linear increase in BPH incidence with increasing age in men over 60 years old [1,2,5]. It is estimated that almost 7 million Caucasian men in the United States (in 2000) have BPH and nearly 8 million physician office visits were made to diagnose BPH [1]. The estimated costs of BPH (in 2000) exceeded $1 billion and approximately 1 in 5 men with BPH had a clinical event, such as prostatectomies, within 1 year of initiating treatment for BPH [1,6]. The symptoms of BPH, (such as nocturia, the most common, causing poor quality of sleep), incomplete emptying, urinary hesitancy, weak stream, frequency, and urgency) can have a significant negative impact on the quality of life [1,2,6]. BPH and prostate cancer has been reviewed in several sources for primary care physicians [7-9].
2. Androgens: BPH

As noted above, the primary changes in prostate disorders are mediated by the conversion of the principle androgen, testosterone, to its more potent metabolite, 5α-DHT [1,2,7-9]. Notably, testosterone’s binding affinity for androgen receptors (AR) is approximately 11 nM while 5α-DHT’s binding affinity for AR is approximately 1 to 3.5 nM [10,11]. This suggests that 5α-DHT’s androgen hormone action is approximately 5-times greater than testosterone and explains, in part, the effects of this potent metabolite in prostate disorders. While somewhat controversial, there is evidence that testosterone levels decline with age in men and may be associated with cardiovascular and other disorders [12-16].

Conversely, there is clear evidence that the 5α-reductase enzymes increase their expression within the prostate with age and disease states [17,18]. This suggests that even though testosterone levels decline with age, the conversion to 5α-DHT increases to influence BPH activation and maintenance of cellular proliferation via the AR [17]. This concept of decreasing testosterone levels but increasing intra-prostatic expression of the 5α-reductase enzymes with aging and the resulting enlargement of the prostate gland is shown in Figure 1. The action of androgens binding to the AR, as well as changes in the 5α-reductase enzymes with BPH and prostate cancer have been reviewed [17-19].

3. Estrogens and BPH

While 5α-DHT has potent actions within the prostate (and other tissue sites), 17β-estradiol is the most potent sex steroid hormone in the body [20]. Estradiol has very high and almost equal affinity for estrogen receptor α (ER-α) and estrogen receptor β (ER-β) via competition binding studies where the Kd is 0.13 nM and 0.15 nM, respectively [21]. Thus, estradiol within the prostate binds equally well both ER-α and ER-β.

Just as the production of prostatic 5α-DHT increases with aging due to the increased expression of the intraglandular 5α-reductase enzymes, there is evidence that the aromatase enzyme that converts androgens to estrogens significantly increases within adipose tissue with aging in men. For instance, in early investigations by Hemsell et al. in 1974, both women and men demonstrated that with advancing age, there is a progressive and significant increase in the efficiency (by 2- to 4-fold) with which androgens are converted to estrogens, suggesting that increased expression of the aromatase enzyme was responsible for these findings [22]. Later molecular biology studies by Bulun and Simpson in 1994 confirmed this notion and extended these findings that aromatase gene expression was greatest in the buttocks and thighs followed by the abdomen with advancing age [23]. Correlations between visceral adipose tissue, increased inflammation and estrogen levels in aging or obese men have been reported [24,25].

However, in 2009 Ellem and Risbridger reviewed the dual, but opposing role of estrogens in the prostate [4]. In brief, they reported that: 1) estrogens are essential for normal tissue homeostasis within the prostate, 2) the importance and differential roles of prostatic ER subtypes and most significantly, 3) activation of ER-α leads to aberrant proliferation, inflammation, and the development of premalignant lesions, while, in contrast, the activation of ER-β is critical in prostatic stromal-epithelial cell signaling and mediates anti-proliferative effects that balance the proliferative action of androgens on epithelial cells [4]. These data emphasize the importance and complexity of estrogen hormone action within the prostate and highlight the known capacity of estrogens to exert both beneficial and adverse effects via ER-β and ER-α, respectively [4] (see Figure 2).

Also, the presence of ERR-γ appears to play an important role in prostate health. ERR-γ is an orphan nuclear receptor whose physiological ligands have yet to be identified. For example, while ERRs are closely related to ERs they do not respond to estrogens [26]. During prostate cancer if ERR-γ is present then this is indicative of a favorable prognosis [3], and ERR-γ has been shown to slow proliferation in breast cancer cell lines [27]. Moreover, ERR-γ suppresses cell proliferation and tumor growth of androgen-sensitive and androgen-insensitive prostate cancer cells [28,29].

Therefore, the importance of estrogens in prostate health cannot be underestimated in light of the beneficial effects of the presence of ER-β and ERR-γ and their positive actions. The combined influence of androgens via
Activating ER-α can have negative effects in the prostate:
- Proliferation
- Malignancy
- Inflammation

Activating ER-β can have positive effects in the prostate:
- Anti-proliferative
- Anti-carcinogenic
- Anti-inflammatory

Figure 2. Estrogen receptor alpha (ER-α) and estrogen receptor beta (ER-β) actions in the prostate. Using a western cowboy theme—the black hat displays negative effects while the white hat displays positive effects. ER subtypes redrawn from [4] with permission.

5α-DHT and estrogens via ER and ERR subtypes needs to be considered in future investigations to reveal the interactions of these chemical/hormone signals as significant prognostic factors in modulating BPH.

4. Current Pharmaceutical Treatments for BPH

A condensation of a larger body of data will be summarized here. Pharmacological management of BPH include selective and non-selective α-blockers (fast acting-hours to days) and 5α-reductase inhibitors (5ARI; relatively slow acting-days to months) for men with symptomatic BPH [2,7,9,18]. In some cases, combination therapy of α-blockers and 5ARIs are employed due to different and complementary modes of action that potentially maximize treatment response or efficacy [2,9]. International prostate symptom scores (IPSS) improve with both modes of pharmacological treatment. However, the most common side effects of α-blockers include: reduced ejaculatory volumes, dizziness, diarrhea, orthostatic hypotension, headache, nasopharyngitis and nasal congestion [2,9,30]. For 5ARIs the most common adverse events are sexual dysfunction including, reduced libido, erectile dysfunction and to a lesser extent ejaculation disorders [2,9]. Also gynecomastia can occur in 1% - 2% of patients with 5ARIs [2,9]. Finally, the goal of therapy is to reduce or alleviate BPH symptoms, to prevent complications, and to minimize adverse effects of treatments [9,31,32].

5. Complementary and Alternative Medicine (CAM): Botanicals-Polyphenols, Isoflavones and Equol

5.1. Polyphenols

CAM agents include polyphenols that represent a wide variety of compounds, which are divided into several classes, e.g., hydroxybenzoic acids, hydroxycinnamic acids, anthocyanins, proanthocyanidins, flavonoids, flavones, flavanols, flavanones, isoflavones, stilbenes, and lignans [33]. An example of a stilbene compound is resveratrol; while in general, isoflavones are soybean-derived products [34] that are found in many food products. Increased research attention directed toward the isoflavonoids in the last 20 - 30 years examined genistein initially that was thought to be responsible for improved prostate health [34-37]. However, since the equol hypothesis was proposed in the late 1990s there has been increased focus on this isoflavonoid molecule [38]. This equol hypothesis suggested that threshold blood equol levels provided increased health benefits for breast, prostate, and other diseases/disorders (see Figure 3).

Polyphenols are abundant micronutrients in the human diet, and evidence for their role in the prevention of certain disorders such as cancer and cardiovascular diseases is continuing to emerge [39-43]. Several thousand molecules having a polyphenol structure (i.e., several hydroxyl groups on aromatic rings) have been identified in higher plants, and several hundred are found in edible plants [33,34,39-41].

5.2. Isoflavones

Soy is the most widely used food product in the world and has been cultivated for over 4000 years where human soy isoflavone consumption has occurred for millennia [44]. Published data by the USDA [45] indicate that isoflavones are components in a wide variety of legumes, prepared foods, spices, teas, and of course, soy food products, including infant formula, tofu, tempeh, cheese, beverages, noodles, sauces, chips and meat substitutes.

The widespread historical exposure to plant isoflavonoids in the diet (by either direct consumption [42,46-54] or secondary consumption via meat and other food products from animals and/or plants) [55-59], is without
adverse human health effects based upon the overall body of available scientific data, which provides compelling evidence of their safety in humans [60].

Also, other data support this notion since isoflavonoid food supplements taken for 2 months had no observable effects on endocrine parameters, testicular volume or semen characteristics at the end of the study and after 4 months of supplementation in men [61]. Furthermore, the developmental status of 1-year old human infants fed soy formula showed normal mental, language and psychomotor development [62] and ultra-sonographic analysis of reproductive organs in 4-month old human infants fed soy formula showed no alterations in reproductive parameters [63]. Finally, the health implications of soy infant formula have been reported [64].

5.3. Equol

Equol, [7-hydroxy-3-(4'-hydroxyphenyl)-chroman], was first discovered in the early 1980s in the urine of human adults consuming soy foods [65]. It was shown to be a key metabolite of daidzein, one of the main isoflavones present in soy foods, and it was formed after intestinal hydrolysis of the soy isoflavone glycoside [66]. Equol, therefore, is naturally produced in the intestine, in humans, as a metabolite of soy foods and some individuals are capable of producing higher levels of equol than others [67].

Most animal species exclusively and efficiently produce equol at high levels when fed diets containing soy [46]. For example, all monkeys, rats, mice, chickens, sheep, cattle, pigs, etc. produced exclusively equol from consuming grass, leguminous plants, clovers, alfalfa and soy-containing supplemental food-derived products to increase the protein content of the feed [46].

However, only about 20% - 30% of humans living in Western countries produce equol after ingesting soy foods, whereas the frequency of “equol producers” in Asian populations that consume soy foods is typically 50% - 60% [46-48,67]. It should be noted that the term “equol-producers” is an arbitrary biomarker set at threshold levels of circulating equol concentrations above 10 ng/ml to 20 ng/ml [68]. The factors for these differences between Western vs Asian populations are unclear [47, 48], but what is apparent is that equol production appears to be a relatively stable phenomenon in humans [21,38, 46-48].

It should be noted that equol production in animals is much higher compared to humans. For example, humans that are considered “equol-producers” display levels around 10 to 200 ng/ml or more, while in all other mammals (except pigs) the levels of equol range between 800 to 2500 ng/ml or more [21,67-70].

The presence of equol in the environment has been reported in manure, topsoil/subsoil, drainage and lysimetric water [71]; this is most likely from run-off from fertilized (manure) fields. Equol levels in humans have been reported in: 1) pregnancy [68], 2) infants [68], 3) children and adolescents [72] and adults [38,40,46,47,52,67]. The presence of equol in humans that are “non-equol-producers” usually range from 1 to 5 ng/ml of equol circulating in their bloodstream. Thus, there are several direct and indirect references of the natural consumption of equol from dietary sources. For example, it is known that equol is contained in the meat and milk products of animals consuming soy-, alfalfa-, or clover-supplemented feeds [33,34,38,46,50,52,54-56]. Also, equol excretion levels correlate positively with the intake of total fat and meat products in humans [50,54].

Further evidence that humans are exposed to equol daily has been reported. For example, equol concentrations in low-soy consuming US populations reflect equol intakes from mammalian (cow) milk sources [73-75] that can be as high as 1.5 mg/kg in cow’s milk [75].

More importantly, equol was recently discovered in plant products. The first study to suggest that equol is present in food products was by Hounsome et al. in 2009 [76]. Subsequent studies by Hounsome et al., in 2010 confirmed the presence of equol in beans, white cabbage and different types of lettuces by Fourier-transform ion cyclotron resonance mass spectrometry [77].

Recent studies by Abiru et al. in 2012 [78] demonstrated that equol is present in other food products. Notably, Abiru et al., measured the equol content of 33 egg yolks where the maximum content was reported to be approximately 130 μg/100g. They also examined 21 different fermented soybean foods. In summary, equol was detected in 28 egg different yolks at the maximum content of approximately 43 μg/100g. In fermented soybean foods, equol was detected only in stinky tofu. They examined 16 stinky tofu samples purchased during different seasons and the average equol content was 1.39 mg/100g, ranging from 0.34 to 2.68 mg/100g [78].

Finally, the most recent report (2013) demonstrating that equol is present in stinky tofu in Asian diets was reported by Jou et al. [79]. They showed that 91% of the 138 stinky tofu dishes contained equol. The mean content per serving (average of 198 grams) was 2.3 + 2.5 mg, the highest being 16.3 mg [79]. Therefore, humans are exposed to this polyphenolic compound from different plant and food sources regardless of age, gender or geographical location with scientific data to support a consumption/exposure record that appears to be safe [60,64, 68].

6. Equol: Anti-Oxidant Properties

Equol is produced in plants and acts as an antioxidant during storage [76]. Notably, the concentration of equol in white cabbage was as high as other isoflavone com-
pounds and known antioxidants and remains stable for months [76]. Comparative studies examining polyphenolic compounds demonstrated that equol is a superior antioxidant, having greater antioxidant capacity than vitamin C or vitamin E in several in vitro tests [80,81]. In fact, in a more recent study, equol exhibited one of the highest antioxidant activities when three different in vitro assays were used and equol was more effective than the positive controls quercetin and ascorbic acid [82]. Finally, in skin studies equol significantly increased superoxide dismutase (SOD 1) and other antioxidant genes while, at the same time significantly decreased inflammatory genes such as the interleukins and cyclooxygenase 1 (COX-1) [83,84].

7. Equol: Anti-Aging Properties and Mechanisms of Action in BPH

Equol, unlike its precursor daidzein (or genistein), is unique in having a chiral carbon atom at position C-3 of the furan ring [21,38,46,68]. It therefore can occur as 2 distinct isomers as S-equol or R-equol. S-equol has been reported to be the exclusive intestinal metabolite of daidzein in all animals including humans [21,38,46,68] but it has been found in plant products like eggs and stinky tufo [78,79]. Notably, the metabolism of R- and S-equol in humans appears to be similar [21,38,85]. Equol is known for its anti-oxidant, anti-inflammatory [72-80] and anti-androgenenic or selective androgen modulator (SAM) activities [86,87].

For example, it was recently demonstrated that both S-equol and R-equol have unique anti-androgenic properties where they both specifically bind 5α-DHT with high affinity [86], and thereby prevent DHT from binding the androgen receptor (AR), acting like a SAM. However, to date, there is no evidence that equol blocks the 5α-reductase enzymes within the prostate (in animals or men). Equol’s SAM activities could be beneficial for prostate health [86], since androgens mediate benign prostatic hyperplasia (BPH) symptoms [1,2].

Equol also has affinity for estrogen related receptor gamma (ERR-γ) and ER-β (to increase positive estrogen-like influences in the prostate). Recall, the presence of ERR-γ during prostate cancer is indicative of a favorable prognosis, and ERR-γ has been shown to slow proliferation in prostate and breast cancer cell lines [27-29]. Using in vitro cultures examining PC-3 cells, equol has been shown to increase the transcriptional activity of ERR-γ [88], thereby enhancing the inhibitory actions of ERR-γ on neoplastic growth [89]. The concentrations of equol required to stimulate ERR-γ are relatively high but not out of physiological range [88] if equol were applied topically or consumed orally.

Finally, it is known that equol (particularly S-equol) has relatively high affinity for ER-β where it can act as a selective estrogen receptor modulator (SERM) [21,38,46,68,86]. Previous laboratories have shown that isoflavones, like equol, binding to ER-β in the prostate can down regulate the AR and thus decrease negative androgen hormone actions [90,91]. Moreover, this may explain how isoflavonoid molecules accumulate in prostate tissue and prostatic fluid after oral supplementation [53,92]. Equol’s SERM-like binding to ER-β within the prostate has positive implications in decreasing proliferation, inflammation and carcinogenesis [4,86] and down regulating ER-α which has a negative impact on prostate health [4]. In part, equol’s powerful anti-oxidant and anti-inflammatory activities may play an important role in this overall mechanism within the prostate which has been demonstrated in human dermal applications [83,84]. A summary of equol’s actions in the prostate is shown in Figure 4.

8. Equol: Treatment of BPH in Men

One pilot intervention study has been reported in evaluating the effects of a low dose oral equol supplement (6 mg, twice a day with meals) for 4 weeks in a total of 18 men (49 - 60 years old) with moderate or severe BPH [93]. Subjects included in the study gave informed consent, underwent a physical examination, verified their BPH symptoms as measured by the International Prostate Symptom Scores (IPSS) and then were assigned to the moderate or severe BPH groups based upon their total IPSS index. All adverse events were reported. The primary efficacy measure was the IPSS parameters compared baseline to 2 and 4 week IPSS indices. Blood samples were collected at the baseline and 4th week visits that served as secondary efficacy parameters that included testosterone, 5α-DHT and general blood chemistries along with cardiac and hepatic function panels. Notably, the safety assessment of R- and S-equol isomer mixtures as a dietary supplement for treating men with BPH has been reported [94].

The results of this study showed a low dose of equol positively improved moderate to severe BPH symptoms according to the IPSS indices. In moderately symptomatic men (n = 10) 5 out of 7 of the IPSS parameters significantly improved by 4 weeks of equol treatment (see Figure 5). In severely symptomatic men (n = 8) all 7 of the IPSS parameters significantly improved with 4 weeks of equol treatment (see Figure 6). There were no significant changes in androgen levels, general blood chemistries or cardiac and hepatic function parameters. However, 5α-DHT levels declined by 21% in severely symptomatic men (from baseline vs. 4 week values).

In examining the evidence that Asian cultures have lower prostate cancer rates compared to Western cultures [34-38,41,46,68,87,93], when data is stratified examining individuals that “produce equol” naturally after soy
Figure 4. Compounds, receptors and mechanisms of how equol works via various pathways to decrease prostate volume and improve BPH symptoms in men. Estrogen receptor beta (ER-β), estrogen related receptor gamma (ERR-γ), estrogen receptor alpha (ER-α), 5α-dihydrotestosterone (5α-DHT), androgen receptor (AR) and white hats represent positive influences while black hats represent negative influences. Redrawn from [92] with permission.

Figure 5. International prostate symptom score (IPSS) values in moderately symptomatic men (n = 10) treated with equol. ▼ = Significant reduction in IPSS values (within a given parameter) at 2 weeks and/or 4 weeks treatment compared to baseline. Redrawn from [92] with permission.

DHT was observed in the severely symptomatic group with oral equol treatment with corresponding significant improvements in prostate symptoms via IPSS values. The reasons moderately symptomatic men did not display any alterations in 5α-DHT levels during the intervention are unknown, but the significant positive influence of the equol treatment on IPSS indices over the course of the study may be due to the other mechanisms of actions outlined above.

9. Equol: Anti-Cancer and Other Disorders

A recent review by Douglas et al. (2013) summarized current human and animal data that provide evidence for several anti-cancer properties of isoflavones in reference to breast cancer [98]. In this regard, one of the first reports on equol as an anti-cancer agent for breast cancer examined case-control studies where there was a substantial reduction in cancer risk with high equol excretion [99]. Later studies by Magee et al. found that equol (particularly R-equol) possessed chemoprotective properties in breast and prostate cells in vitro [96,100]. In fact, equol has been reported to enhance tamoxifen’s anti-tumor activity by induction of caspase-mediated apoptosis in MCF-7 breast cancer cells [101]. Also, there is evidence that being an “equol-producer” has clinical benefit in protection against breast cancer [38,102]. As a final point, equol has been reported to be a DNA methyltransferase-1 inhibitor that may be an epigenetic therapy for cancer [103].

In reference to prostate cancer, as reported by Akaza et al., the ability to be an “equol producer” or the administration of equol itself is closely related to a lower incidence of prostate cancer [95]. Equol is also known to inhibit invasion in prostate cancer cells due to a down-regulation of matrix metalloproteinases (MMPs) [104],
which corresponds with human dermal studies that displayed similar findings of equol inhibiting the gene expression of MMPs [83,84].

Finally, Richardson and Simpkins have reported that equol could have beneficial effects in delaying the onset and decreasing the severity of symptoms in Friedreich’s ataxia patients by an antioxidant mechanism unrelated to binding estrogen receptor subtypes [106]. Thus, there are several reported studies that suggest equol has chemoprotective properties from both in vitro and clinical studies.

10. Conclusion

BPH is the pathological cellular progression of glandular proliferation associated with aging affecting millions of men usually over the age of fifty in the US and worldwide. The primary changes in BPH are mediated by $5\alpha$-DHT. However, recent evidence suggests that estrogen hormone actions via estrogen receptor subtypes (ERR-$\gamma$ and ER-$\beta$) also play important roles in BPH. Current pharmaceutical options for BPH like selective and non-selective $\alpha$-blockers and $5\alpha$-reductase inhibitors have advantages, limitations and adverse effects. CAM treatments for BPH include botanicals such as polyphenols and isoflavones. Equol is a polyphenolic/isoflavonoid molecule derived from intestinal metabolism, dairy and dietary plant sources. Equol has potent anti-oxidant, anti-inflammatory, anti-androgenic and positive estrogenic properties (via ERR-$\gamma$ and ER-$\beta$) to decrease prostatic irritation and potentially neoplastic growth. The clinical efficacy of equol to significantly decrease BPH symptoms is presented. The beneficial clinical efficacy of equol observed may be due to the multiple positive biological actions that are not present in current pharmaceutical treatments. Finally, equol appears to have chemoprotective effects and cyto-protective effects in Friedreich’s ataxia.

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