fermentation

MDPI

Review

The Role of Probiotics and Synbiotics on Hirsutism

Vasiliki Lolou

Department of Applied Sciences, Northumbria University, Newcastle Upon Tyne NE1 8ST, UK; vasiliki.lolou@northumbria.ac.uk

Abstract: Probiotics and synbiotics are known to have beneficial effects on human health and disease. Hirsutism, a disorder that is characterised by the presence of coarse terminal hairs in a male-like pattern, is usually caused by elevated androgen levels in blood plasma. This disorder is usually observed in PCOS women and it is linked to insulin resistance (IR). Although idiopathic hirsutism (IH) is not shown to have excess androgen production from the ovarian and adrenal glands, increased 5α-reductase in peripheral tissues and insulin resistance are common observations. The effect of probiotics and synbiotics have been recently studied on PCOS women; androgens were also included in the hormonal groups that were investigated. Only a few studies focus on hirsutism and the potential effect of the beneficial microbes mentioned, whereas the increasing interest on insulin resistance and synbiotics indicate a potential beneficial effect on hirsutism through the management of insulin resistance.

Keywords: probiotics; synbiotics; hirsutism; androgens; insulin resistance; PCOS

1. Introduction

Fermented food, such as yoghurt, bread, bear and wine, has been widely known since ancient times, and some have been used since then, for therapeutic purposes [1–3]. Fermented dairy products (yoghurt, kefir) were used to treat diseases like diarrhea and other infections of the intestinal tract [4,5]. Interaction between microorganisms and human health was first reported in 1907, where yoghurt microflora was described by Elie Metchnikoff [6]. Fermented food is still used as an additional treatment for disease, such as wounds [7–9], gastroenteric disorders and infections [7,10], as well as an overall support for health [7,8,10–12]. The term probiotic was introduced by Werner Kollath [13] and according to the World Health Organisation (WHO), this term refers to the microorganisms that ''when administered in adequate amounts, confer a health benefit on the host'' [14]. Probiotics are found to have multiple beneficial roles on human health and disease, through restoration of gut microbiota (GM) [15,16], symptom improvement on intestinal disease, such as irritable bowel syndrome (IBS) [17], modulation of hormonal profile in animals and humans [18–22] and skin infections and healing [23–25]. Along with the beneficial microorganisms, prebiotics, which are fermented compounds that support and promote modifications in the activity and composition of GM [26], have also been studied. It is shown that a controlled combination of probiotics and prebiotics, called synbiotics, can provide a more enhanced beneficial effect on human health and disease [16,27–29].

Although the effect of probiotics and synbiotics are extensively studied, there has been limited research conducted on their effect on sex hormones and sex hormone imbalances, such as hirsutism, a disorder that is mainly characterised by elevated androgen levels in women. The aim of this review is to focus on the role of probiotics and synbiotics and their metabolic process on hirsutism.

1.1. Probiotics

Lactobacillus, *Streptococcus*, *Bifidobacterium*, *Lactococci* and *Saccharomyces* are some of the probiotic species that are known [30]. Microorganisms that are mostly used as treatments

check for updates

Citation: Lolou, V. The Role of Probiotics and Synbiotics on Hirsutism. *Fermentation* **2021**, *7*, 10. https://doi.org/10.3390/fermentation7010010

Received: 13 December 2020
Accepted: 8 January 2021
Published: 11 January 2021

are *Lactobacillus*, *Streptococcus*, *Bifidobacterium* and *Saccharomyces*, whilst most of them are naturally present in the human GM [31–37]. There has been an increase in research on the effect of probiotics on health and disease, whilst they are shown to have both beneficial effects on healthy subjects and therapeutic effect on various diseases and conditions, such as intestinal disease [38–46], skin disease [10,24,47–52] and wound healing [53–57]. Probiotics have also been used for the restoration of disturbed GM [58]. Dysbiosis of gut microbiota (DOGMA) is the alteration of gut microflora that can occur due to a variety of reasons, such as antibiotic use [59,60] and diet [61,62]. The human gut, also described as the "second brain" of the human body, plays an important role in human health and disease [63,64]. The GM is known to have a significant role in the functionality of the bowel, maintaining the gut mucosa through their role on gut homeostasis [63–65]. The probiotic *E. coli* Nissle 1917 protects and prevents against inflammatory response via TLR-4 and TLR-2-dependent pathways, whilst lower counts of *Firmicutes prausnitzii* are linked with potential inflammatory bowel disease pathogenesis due to its anti-inflammatory effects [65,66]. The impact of the metabolic processing of the gut microflora in the gut is extended outside of the bowel and can impact other functionalities of the human body, reaching the skin [10,24,67–69]. *L. casei* is shown to reduce skin inflammation through the regulation of $CD8^+$T cells, which initiate inflammatory response [47]. The role of probiotics on endocrinology has also been reported and GM was shown to affect the production of hormones, such as leptin [62,70,71], stress hormones [72], insulin [73,74] and sex hormones [75,76] in the intestinal tract. Additionally, the disturbance of gut microbiota can affect the levels of endogenous hormones, such as estrogens, as well as administrated steroids, such as megestrol acetate, medroxyprogesterone acetate, norethisterone and others, suggesting that the use of antibiotics can cause hormonal imbalance and reduce the absorption of contraceptive hormones, which are used as a method of birth control and/or treatment for metabolic syndromes [75]. An altered microbiota during the early life of the diabetic mouse (Type 1) can determine sex hormones and cause metabolic changes, such as increased testosterone levels [76]. Administration of probiotics can restore the imbalanced microorganisms that live in the human intestine and improve certain conditions through their metabolic processes [58]. Additionally, DOGMA is also observed in patients suffering from inflammatory bowel disease, colitis [77], Crohn's disease, IBS [63], polycystic ovary syndrome (PCOS) [78] and other conditions.

1.2. Synbiotics

Synbiotics are the controlled combination of probiotics and prebiotics and their supplementation aims to provide a more enhanced health benefit on human health and disease. Known prebiotics are fructans (e.g., inulin), complex polysaccharides, oligosaccharides and sugar alcohols [16,79] and in combination with probiotics, they have been used for the treatment of conditions and disease [18,27,28,80,81]. Synbiotics containing *L. acidophilus NCC90*, oligofructose and acacia gum can have a preventive role on bone mineral loss after ovariectomy in rats [16]. It has been reported that synbiotic treatments showed beneficial effects on non-alcoholic fatty liver disease (NAFLD), reducing fibrosis and hepatic steatosis in humans [82,83], total necrosis factor α (TNF-α), total nuclear factor κ-B (TNF-κB) and other NAFLD biomarkers, such as high-sensitivity C-reactive protein [83]. Moreover, synbiotics can bring improvements on Crohn's disease through reduction in TNF-α production [84], IBS [85] and delayed Alzheimer's disease in *Drosofila melanogaster* [86]; improvement of thyroid function was observed after 8 weeks of synbiotic supplementation in hypothyroid patients, decreasing thyroid stimulating hormone (TSH) levels and increasing tri-iodothyronine (FT3), whilst overall increasing FT3/TSH ratio [18]. *Bifidobacterium Longum* in combination with inulin, reduced levels of TNF-α and IL-1α in patients suffering from ulcerative colitis [77]. Another study on patients with ulcerative colitis showed that *B. breve* and galacto-oligosaccharide (GOS)-containing beverage (Yakult) managed to clinically improve the condition of the patients, through reduction of UC markers, such as myeloperoxidase, and by lowering the faecal pH [87].

1.3. Hirsutism

Hirsutism is a condition that appears in 5–10% of women and it is recognized by the presence of coarse terminal hairs in a male-like pattern [88]. Excess hair growth that consists of terminal hairs are present in areas were women normally have thinner hair. The clinical diagnosis of hirsutism is completed based on Ferriman and Gallwey criteria (Figure 1) [88] and the areas that are scored include the face, chest, thighs, upper arms, abdomen and back. Scores (m-FG) from 1–4, with 1 describing minimal terminal hair and 4 describing frank virilization, are given to the mentioned areas whist total scores less than 8 are considered normal [88].

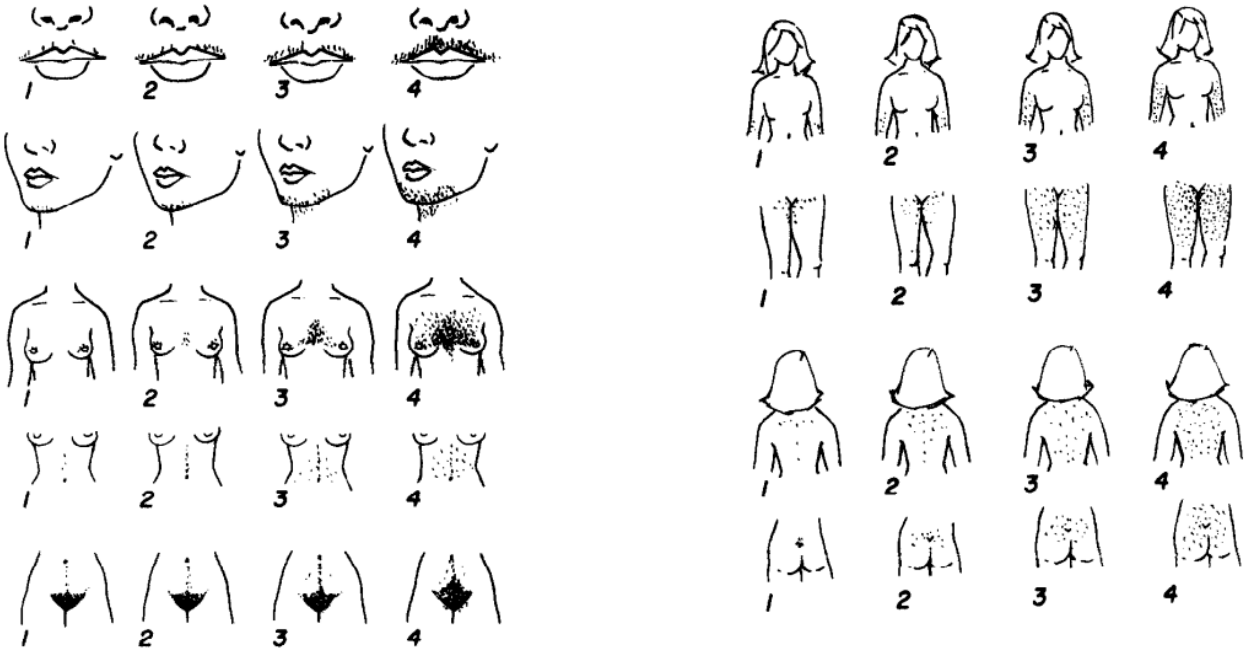

Figure 1. Hirsutism scoring system presenting scores ranking from 1—minimal hirsutism, to 4 virilization in 9 body parts. A total score of less than 8 is considered normal, whereas higher scores indicate mild to severe hirsutism [88].

Hirsutism is a quite complex condition that can occur due to other syndromes or disease, such as PCOS (Figure 2). Although the main reason for this condition is the presence of excess androgens, such as testosterone (T) and dihydrotestosterone (DHT), IH shows normal levels of androgens [89,90]. The most common reason for the excess androgen levels is PCOS and 60–80% of PCOS women suffer from hirsutism [91]. The diagnosis of this condition is conducted according to the Rotterdam criteria, by which two of the three criteria have to be met: (a) evidence of hyperandrogenism, (b) oligo- and/or anovulation and (c) polycystic ovaries [92]. Other clinical features are ovarian enlargement and IR, which is found to be very common amongst PCOS women, whilst the syndrome has also been linked with cardiovascular disease and inflammation. The heritability of this disorder has been studied and it is possible that genetic changes on the androgen receptor gene can lead to hirsutism [90]. During this study, a repeatability of the trinucleotide CAG in exon 1 was observed and more frequent repeats in the N-terminal domain of the androgen gene were linked with the development of the disorder. However, other researchers have not shown a significant role of CAG in the pathogenesis of hirsutism [93,94]. Hirsutism has also been linked with IR (Figure 3) [91,95–101], whilst excess insulin production leads to hyperinsulinemia, which increases luteinizing hormone (LH) through insulin receptor stimulation [97]. LH, along with follicle-stimulating hormone (FSH), is a hormone that regulates androgen production through the secretion of them from ovarian and adrenal glands. Moreover, high levels of insulin inhibit sex hormone-binding globulin (SHBG), a hormone that binds with plasma T and is considered its major determinant along with 17-β hydroxysteroids from plasma [102]. Consequently, both

effects of IR are directly linked with hirsutism through excess androgen production. This relationship between IR and hirsutism was studied in healthy women, where adipose tissue was collected and in-vitro treatments with testosterone and/or anti-androgens were conducted on insulin stimulated adipose cells [100].

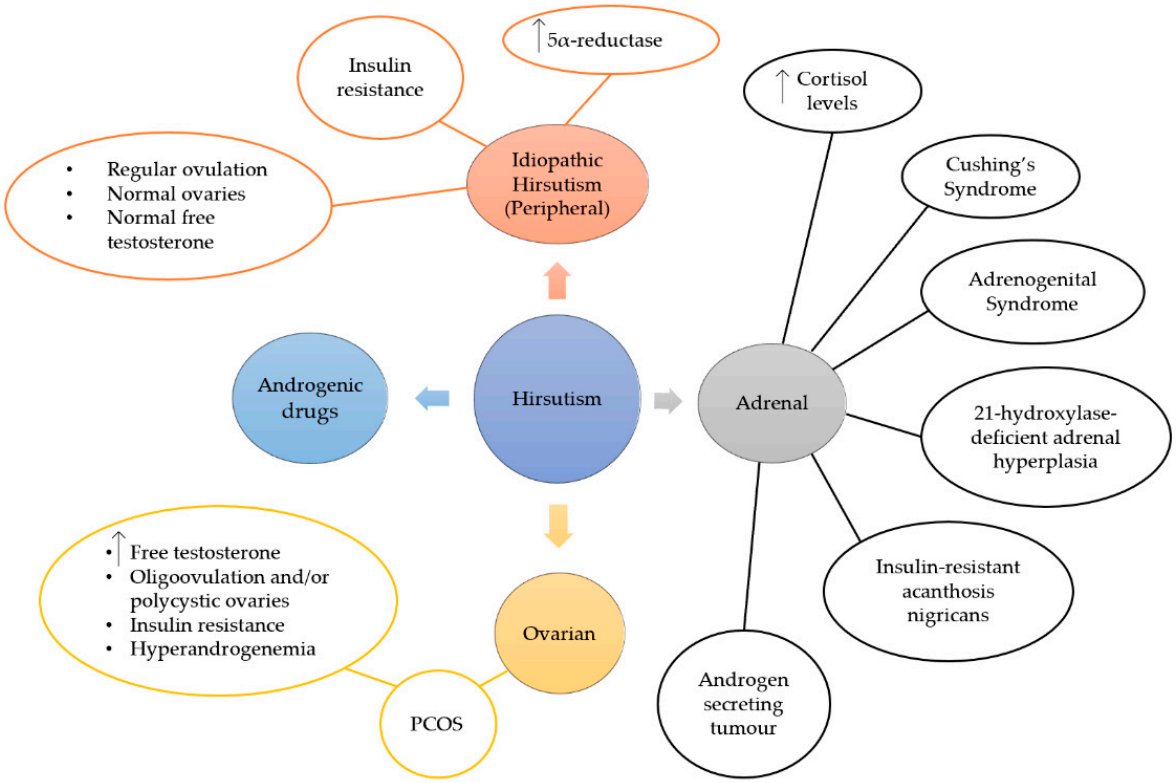

Figure 2. Hirsutism can originate from adrenal or ovarian disorders, or both. Various syndromes and disorders related to the adrenal glands, such as Cushing's syndrome, adrenogenital syndrome, 21-hydroxylase-deficient adrenal hyperplasia, insulin-resistant acanthosis nigricans and androgen secreting tumour, show high levels of cortisol hormone and hirsutism. Ovarian hirsutism is caused by PCOS that is characterised from high levels of free testosterone and/or polycystic ovaries, insulin resistance and hyperandrogenemia. Idiopathic hirsutism is caused by peripheral increase of androgens, and women that suffer from it show increased levels of 5α-reductase and insulin resistance, whilst they do not show any abnormalities in their ovarian or adrenal function.

Adipose tissue contains adipocytes, also known as fat cells and are responsible for fat energy storage. This study showed that the exposure of these cells to testosterone led to insulin resistance, suggesting there is a link between hirsutism, androgen presence and insulin resistance development.

Other disorders that are known for the increased production of androgens are hyperandrogenic insulin-resistant acanthosis nigricans syndrome [103,104], 21-hydroxylase-deficient non-classic adrenal hyperplasia [90,105], androgen-secreting tumor [106], and rarely androgenic drug intake [107]. On the other hand, the causes of IH are not well known. However, when hormonal profiles of PCOS women and IH women were compared, IR was found to be significant in both groups compared to the control group. IR and hyperinsulinemia increase the insulin-like growth factor (IGF) which affects hair follicles [95,96], and therefore it is suggested that IR is potentially a cause of IH. This disorder is also characterised as an increase in 5α-reductase in peripheral tissues, an enzyme that converts T to DHT, and is generally responsible for the metabolism of steroids [95]. Potential causes of IH include increased sensitivity of hair follicles to androgens, and androgen receptor gene polymorphism [96].

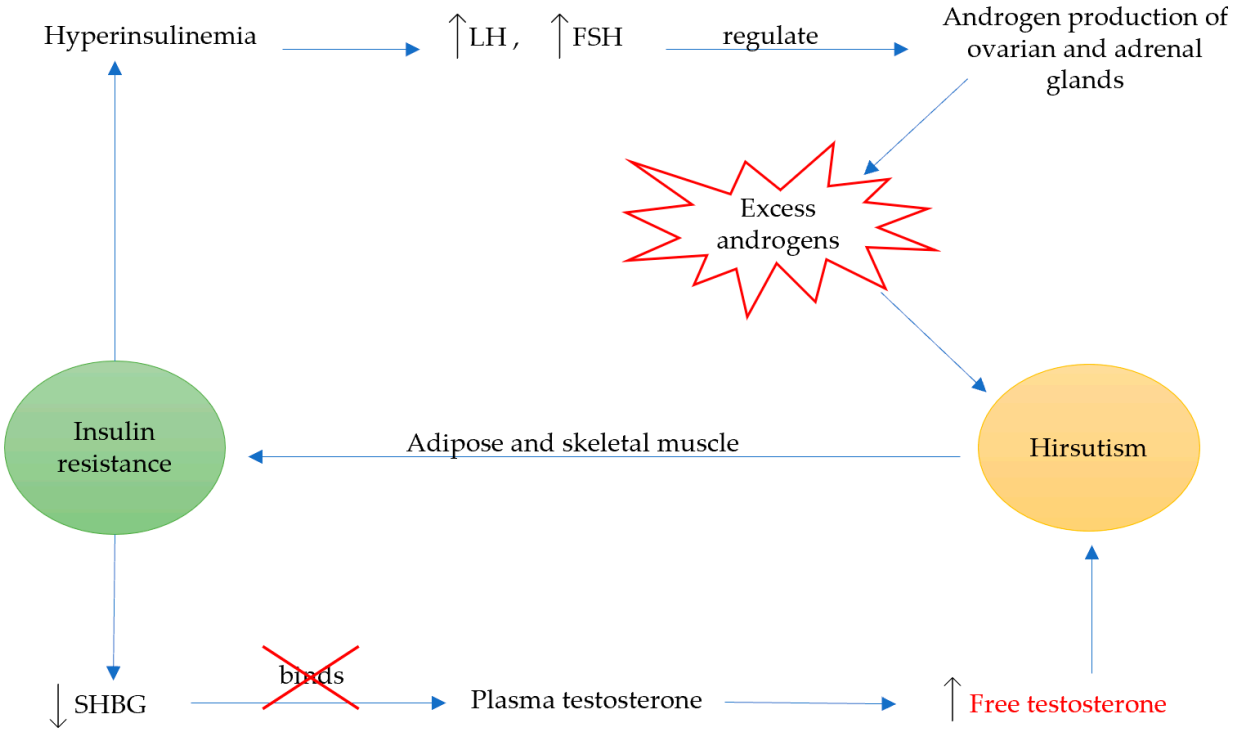

Figure 3. The relationship between insulin resistance and hirsutism. Hyperinsulinemia is caused when insulin resistance is left unmanaged, causing an increase in LH and FSH, which regulate the production of ovarian and adrenal androgens. This increase results in excess androgens, and eventually hirsutism. Moreover, insulin resistance reduces SHBG, which leaves plasma testosterone unbound leading to increased free testosterone and hirsutism. Chronic androgen exposure leads to adipose and skeletal muscle insulin resistance. The graph above presents the circular relationship between the two conditions, leading to a vicious cycle of effects.

2. Therapeutic Index

Hirsutism treatments are usually combinational treatments, and they include peripheral androgen blockage, androgen suppression and cosmetic intervention. Cosmetic and mechanical interventions are more effective and long lasting when used in combination with either androgen suppression treatment or peripheral androgen blockage. Moreover, alternative treatments have been investigated in recent years and naturally derived additional treatments have been used for the improvement of hirsutism, as well as live organisms that are shown to have a significant role in regulating and reducing androgen production on PCOS women.

2.1. Chemically Derived Therapies

Current drug therapies for hirsutism include androgen suppression and peripheral androgen blockage, also known as anti-androgens. For a more effective treatment these drugs are usually administered in combination [108–112].

Androgen suppression treatments include insulin sensitisers, long acting gonadotrophin releasing hormone (GnRH) analogue and estrogen-progestin oral contraceptive (OC) pills [98,112–114]. OC action can differ in composition, but it is not shown to significantly influence the effectiveness of the treatment. Their compositions can be monophasic, biphasic or triphasic and the action of the OC is through the suppression of LH and FSH and therefore a reduced androgen production from the ovaries [90]. Although this treatment is shown to reduce SHBG and hyperandrogenemia in general, it does not have an effect in low-grade inflammation and other hormonal disorders. Third generation OCs are not as effective at reducing the levels of SHBG when compared to older combined OC [115]. OCs containing sex hormones progestin and estrogen are shown to have significant effect on the hormonal profiles of hirsute women, reducing the levels of androgens, such as T, dehy-

droepiandrosterone sulfate (DHEAS) and DHT [116]. GnRH is a hormone produced in the hypothalamus and it stimulates the production of LH/FSH which stimulates the ovaries to produce androgens [97]. GnRH analogues are antagonists of GnRH and, when used on PCOS women, were shown to reduce the total and free T, DHEAS and androstenedione sex hormone. This treatment is usually combined with OCs. Moreover, the combination of insulin sensitisers with OC has also been studied. Insulin sensitisers, such as metformin and thiazolidenediones, are shown to reduce androgen production through the regulation of blood glucose and the increase of insulin sensitivity [108,112,117,118]. Metformin has been widely used, alone or in combination with other OCs or anti-androgens, for the treatment of PCOS as it is shown to decrease levels of LH, testosterone, and androstenedione, and improve the ovulation and decrease IR [108,109,112,113,119–122]. Metformin is shown to be equally but moderately effective on reducing the hair diameter in PCOS women when compared to anti-androgen combined with OC [112]. Although there was no decrease of androgen levels, the effect is suggested to appear due to the reduction of hyperinsulinemia. This suggests that managing insulin resistance and increasing insulin sensitivity might be a better therapy treatment and approach, than administrating anti-androgens. Overall, the combination of metformin with other drugs appears to be more effective on the treatment of hirsutism, decreasing m-FG scores, levels of androgens and further drop of free androgens through the enhancement of SHBG [109].

Peripheral androgen blockage drugs include cyproterone acetate, spironolactone, flutamide and bicalutamide. 5α-reductase inhibitors, such as finasteride, have also been used for the treatment of hirsutism [123]. These drugs bind to the androgen receptors in selective tissues and therefore reduce the synthesis of androgens [124–126]. Cyproterone acetate is shown to be effective in treating excessive hair growth and reducing androgen levels [100,110,112,123,124,127,128], although side effects, such as weight gain, tiredness, loss of libido and adrenal disfunction were reported [127–129]. The effect of this progestogenic drug is through the inhibition of gonadotropin response to reduce T levels, decrease hair growth and androgen levels [127,128,130]. Spironolactone was originally used as a diuretic drug. However, it was shown to reduce T, through cytochrome P450 inhibition, without having any effect on SHBG or free T [131]. It is shown to be an effective and tolerable drug for the treatment of hirsutism, especially when combined with OC [132–134]. Flutamide is reported to be a better choice of treatment for the disorder studied when compared to the previously mentioned drugs [134]. It is shown to have a significant effect on hirsutism, acne and male-pattern hair loss in hirsute women. However, severe side effects are reported, such as embryotoxicity, thus it is suggested to use in combination with other drugs, such as insulin sensitisers or OC [98,108,111,122,134]. Bicalutamide was shown to have similar effectiveness with the above drugs on reducing m-FG scores and lower androgen levels, although it did not have any effect on insulin resistance [135–137]. Despite the effectiveness of these drugs, many subjects are sceptical when it comes to the administration of such treatments due to the potentially severe side effects. Thus, the potential therapeutic effect of naturally derived therapies is also studied.

2.2. Naturally Derived Therapies

Many natural remedies have been studied and used for the management of hirsutism and acne, however, extensive research has not been conducted for many of them [138–141]. Some of the naturally derived anti-androgens are spearmint tea, green tea, licorice, Chinese peony, marjoram, and red reishi [141]. In a study where the effects of spearmint tea as an anti-androgen were investigated, forty two patients were asked to consume two cups of spearmint tea every day for thirty days [142]. Their gonadotrophin levels and androgen hormones were tested before and after the treatment and a significant reduction of total and free T was observed. Increased LH and FSH were also observed after short administration with spearmint tea [140]. Marjoram is shown to significantly reduce levels of DHEAS and improve IR, and therefore inhibit the production of androgens [143]. Diet has also been investigated on the role of hormonal imbalances especially since the production of

androgens is related to IR. Studies are still at early stages, looking at the potential effect of dairy and starch on the hormonal profile of PCOS women [144–146]. Studies where women were asked to follow a low starch and low dairy diet presented mixed results and the role of these foods on hormonal profiles requires more research. In addition to plant-based remedies and diet for the treatment of hirsutism and other hormonal imbalances, live organisms have also been studied on their potential effect on the hormonal profile of hirsute women [147–151].

2.2.1. Probiotics and Hirsutism

Microbes have been widely used for the production of various chemicals in the pharmaceutical world. In a recent study, after metabolically engineering *Rhodococcus ruber Chol-4*, it was shown to produce high amounts (61%) of testosterone through the conversion of 4-androstene-3,17-dione (AD) to the mentioned hormone [152]. There is increasing literature on how probiotics can affect the hormonal profiles in animals and humans and how probiotic supplementation can be used for the management and improvement of metabolic disorders and conditions. When the GM taxa of boards and gilts was analysed, host sex hormones were shown to significantly interact with the GM, which indicates the relationship between hormones and microbes [20]. Another research study that presents the relationship between the gut microbiota and the hormonal balance, is when the androgen levels of normal GM mice were compared to germ-free mice and findings showed exceptionally low unconjugated DHT detected in the later subject's distal intestine in contrast with the former subjects [153]. Interestingly, in the same study, human male feces samples with normal GM were tested and similar findings were observed compared to the normal GM mice samples. For the mice samples, male and female subjects were included. It is therefore proposed that treatment with probiotics could potentially affect the levels of DHT and T.

As mentioned earlier, PCOS is the most common cause of Hirsutism and most women that suffer from this syndrome show symptoms of increased hair growth in a male-like pattern. There is growing literature on the role of probiotics on PCOS and how the mentioned microbes are potentially involved in the management of this condition. Tremellen and Pearce in 2012 presented a detailed hypothesis on the development of PCOS starting from dysbiosis of gut microbiota (DOGMA) and how this causes a series of effects that eventually leads to hirsutism along with other symptoms of PCOS [154]. More specifically, it is hypothesised that the disruption of the balance of GM, and in combination with a diet high-in- sugar and saturated fat, leads to increased gut mucosa permeability. This allows the gram-negative bacteria to enter the systemic circulation and stimulate the immune system causing mild chronic inflammation, leading to damage in insulin receptors that further develops into IR and hyperinsulinemia in the long term. The latter condition affects the ovaries to produce excess androgens and disrupts their normal function, causing further disturbance in the development of follicles. Therefore, it is possible to hypothesise that these conditions are less likely to occur if a well-balanced gut microbiota is maintained. The above hypothesis was further investigated a few years later, where the potential gut permeability, and the level of inflammation and GM in PCOS women was studied [155]. Even though the GM was indeed found to be altered, compared to healthy subjects, there was no significant changes in gut permeability and function suggesting that "leaky" gut is only potentially a symptom in women with PCOS. In another study where the relationship of PCOS and gut microbiota was investigated, PCOS rats' GM was compared to control groups and a decreased number of *Lactobacillus*, *Clostridium* and *Ruminococcus* were detected, whereas *Prevotella*, a gram-negative bacteria, was found in higher numbers than for the healthy subjects [156]. The rat's PCOS was induced using an aromatase inhibitor called letrozole and the subjects showed increased levels of androgens along with symptoms of abnormal hormonal levels and cycles with their ovaries morphologically altered. To further investigate this relationship, faecal microbiota and *Lactobacillus* were transplanted in the gut of PCOS rats and restoration of the gut microbiota was observed along with improvement of PCOS symptoms. Interestingly, the androgen levels were reduced, and

the ovaries' morphology was improved. Such effects are in agreement with more recent studies where androgen levels and hirsutism are shown to improve after supplementation with probiotics [148,149,157]. Possibly the first investigation on hormonal profiles of PCOS women after the supplementation of probiotics, was presented in 2018 in a study where 60 women participated [157]. Probiotics *Lactobacillus* and *Bifidobacterium*, two of the most common species used in probiotic treatments, were supplied to the subjects for 12 weeks after which time significant increase in SHBG was observed, whilst m-FG scores and total testosterone were decreased. Combinational treatments of vitamin D and probiotics also showed a significant response when it comes to androgen level reduction [149]. Although this suggests that probiotics might be more efficient on managing hirsutism when combined with vitamin D, other researchers have not shown any significant effect of the vitamin alone to the referred condition [158–161], despite its significant anti-inflammatory and insulin sensitivity effect [162–164]. Therefore, it is possible that the effects of the combinational treatment are due to the improvement of IR from vitamin D, along with the probiotics effect [149]. It is also reported that PCOS-rats showed improvement in reproductive function after the treatment with probiotics [165]. Although only a few studies have looked at the effects of probiotics on hirsutism, the literature found on the role of the former on IR and sensitivity has been explored in several studies [27,165–173]. Moreover, it is now well established from a variety of studies that hirsutism is linked with IR [21,95–97,104,174–177]. As described earlier IR and hyperinsulinemia enhances the production of androgens such as T and DHT, whilst reduces SHBG levels leading to increased free testosterone levels [102].

Considering the above it is necessary to briefly present the role of probiotics on IR through which a potential improvement of hirsutism can occur. Research has been conducted on PCOS subject as well as prediabetics and healthy participants. In 2015, Shoaei et al. studied PCOS women for 8 weeks while the subjects were under probiotic supplementation, observing decreased FBS, insulin levels and IR [173]. The same observations were made in another study conducted on PCOS women where probiotics were supplemented for 12 weeks [167]. Glucose levels decreased during pregnancy and insulin sensitivity increased during the 12 month postpartum period, in a study where subjects were treated with *Lactobacillus* and *Bifidobacterium* [168]. Lower glucose levels were also observed when post-menopausal women were provided with *Lactobacillus plantarum*-containing beverages [170]. It is reported that *Lactobacillus salivarius UBL22*, when supplemented on healthy subjects, showed a significantly reduced fasting insulin compared to the control group (placebo) [27]. Another study conducted on prediabetic participants showed a reduction in fasting glucose and fasting insulin levels after treatment with probiotics (Table 1) [166].

Table 1. Probiotic treatments and the hirsutism-relevant outcomes.

Treatment	Study Population	Relevant Outcomes	Reference
Lactobacillus	PCOS [1] rats	Improvement on estrous cycles, reduction of androgen biosynthesis, normalization of ovaries, GM [2] restoration, reduction of *Prevotella*	[156]
L. acidophilus, *L. casei*, *B. bifidum*	PCOS women	Reduction of total testosterone, increase of SHBG [3], decrease of m-FG scores	[157]
L. acidophilus, *L. reuteri*, *B. bifidum* and Vitamin D	PCOS women	Reduction of total testosterone and hirsutism	[149]

Table 1. *Conts.*

Treatment	Study Population	Relevant Outcomes	Reference
E. faecali, *L. reuteri*, *Bifidobacterium*	PCOS rats	Improvement in reproductive function and GM restoration	[165]
L. acidophilus, *L. casei*, *B. bifidum*	PCOS women	Reduced fasting plasma glucose, insulin concentrations and insulin resistance. Increased insulin sensitivity	[167]
L. acidophilus, *L. casei*, *L. rhamnosus*, *L. bulgaricus*, *L. breve*, *B. longum*, *S. thermophiles*	PCOS women	Reduced FBS [4], reduced insulin levels and reduced insulin resistance	[173]
L. plantarum	Postmenopausal women	Reduced glucose levels	[170]
L. rhamnosus, *B. lactis*	Postpartum period women	Reduced blood glucose concentrations, improved glucose tolerance, reduced insulin concentrations and increased insulin sensitivity	[168]

[1] polycystic ovary syndrome; [2] gut microbiota; [3] sex hormone-binding globulin; [4] fasting blood sugar.

2.2.2. Synbiotics and Hirsutism

In reviewing the literature, very few studies were found on the association between synbiotics and hirsutism. A recent study looked at the effects of synbiotics on PCOS women using a mix of pomegranate juice, inulin and *Lactobacillus* [178]. Testosterone levels were significantly reduced after the treatment with synbiotics, compared to the control group. These findings were accompanied with an increase in insulin sensitivity and improved anthropometric measurements. Inulin is a prebiotic that has been shown to improve IR and has a beneficial effect on SHBG [147,179,180]. In a 12 week study, *Lactobacillus bifidum*, *Lactobacillus acidophilus*, *Lactobacillus casei* and inulin were used for the treatment of PCOS women and their hormone levels were studied along with other biomarkers, such as serum high sensitivity C-reactive protein [19]. Despite the statistical significance of the decrease of m-FG scores, the clinical picture of the subjects showed little improvement and longer treatment with prebiotic inulin was suggested. Selenium, known for its prebiotic activities [181–183] was also used in a combinational treatment with probiotics on women and the hormonal profiles were studied [150,184,185]. Although initial studies have not shown an effect of the treatment on free [184] and total [185] testosterone, a decrease on m-FG scores was observed [184]. On a 12-week study conducted two years later, 60 PCOS subjects were treated with *Lactobacilllus*, *Bifidobacterium* and selenium-containing synbiotics and, in contrast with the above findings, a statistically significant reduction of total testosterone and hirsutism was shown [150]. There is abundant room for further progress in determining the exact effect of synbiotics on hirsutism, whilst there is an increasing literature on the beneficial effects of synbiotics on IR on PCOS women.

Brief investigation of the role of synbiotics on IR is necessary to understand how synbiotics could potentially improve hirsutism through the improvement and management of IR. A year after Nasri et al. (2018) published their work as described earlier, Samimi et al. (2019) investigated the effects of the same synbiotics supplementation on biomarkers of IR and sensitivity along with cholesterol and triglycerides on PCOS women [180]. In this study, it was shown that *Lactobacillus bifidum*, *Lactobacillus acidophilus*, *Lactobacillus casei* and 0.8 g of inulin, significantly improved insulin metabolism markers but not FBS, after 12 weeks of treatment, suggesting that metabolic disorders can benefit from the mentioned

treatment while managing symptoms. Longer treatment periods (24 weeks) were also investigated and prediabetic adults were treated with *Lactobacillus* and *Bifidobacterium* in a inulin-containing prebiotic [166]. There was no significant improvement on fasting insulin levels and plasma glucose between the two studied time points, 12 and 24 weeks. The use of a single probiotic along with inulin is found in a study that was conducted on diabetic rats and their insulin markers were observed [80]. The synbiotic containing *Lactobacillus plantarum* and inulin managed to increase insulin sensitivity. All the above studies described were conducted on subjects that were either diagnosed as prediabetics or suffered from conditions (PCOS) for which IR is known to be a symptom. However, the beneficial effect of synbiotics was also observed when healthy subjects were treated with *Lactobacillus salivarius UBL S22* and FOS and the treatment was shown to improve insulin sensitivity significantly more compared to the probiotics alone [27]. Interestingly, despite the higher variation of probiotic bacteria in the synbiotic mix (*Bifidobacterium breve*, *Lactobacillus casei*, *Lactobacillus bulgaricus*, *Lactobacillus rhamnosus*, *Bifidobacterium longum*, *Lactobacillus acidophilus*, *Streptococcus thermophilus*), in combination with the fructo-oligosaccharide inulin on PCOS women, it does not show a significant effect on the FBS and insulin sensitivity [179]. *Lactobacillus* synbiotics and 200 µg/day selenium [186] were used for the treatment of PCOS subjects for 12 weeks and it was found to improve IR and insulin levels, findings that were not observed when selenium alone was used for the treatment of diabetic participants [187]. Other studies show similar observations on fasting plasma glucose [188] and insulin levels, IR and insulin sensitivity (Table 2) [189].

Table 2. Synbiotic treatments and the hirsutism-relevant outcomes.

Treatment	Study Population	Relevant Outcomes	Reference
Lactobacillus and pomegranate juice	PCOS [1] women	Reduced testosterone levels, increased insulin resistance and improved anthropometric measurements	[178]
L. bifidum, *L. acidophilus*, *L. casei* and inulin	PCOS women	Reduced m-FG scores but did not affect the clinical picture of hirsutism	[19]
Lactobacillus, *Bifidobacterium* and Selenium	PCOS women	Reduced total testosterone and hirsutism	[150]
L. bifidum, *L. acidophilus*, *L. casei* and inulin	PCOS women	Improved insulin metabolism markers but did not influence FBS [2]	[180]
Lactobacillus, *Bifidobacterium* and inulin	Prediabetics	Decreased fasting insulin levels and fasting plasma glucose	[166]
L. plantarum and inulin	Diabetic rats	Improved insulin resistance, hypothalamic levels of insulin and leptin	[80]
L. salivarius UBL S22 and fructo-oligosaccharides	Healthy participants	Improved insulin sensitivity	[27]

Table 2. *Conts.*

Treatment	Study Population	Relevant Outcomes	Reference
L. bulgaricus, *L. acidophilus*, *L. casei*, *L. rhamnosus*, *B. longum*, *B. breve*, *S. thermophilus* and inulin	PCOS women	No effects on fasting insulin levels	[179]
L. acidophilus, *L. reuteri*, *L. fermentum*, *B. bifidum* and selenium	PCOS women	Reduced insulin levels and insulin resistance. Increased insulin sensitivity	[186]
L. acidophilus, *L. casei*, *B. bifidum* and inulin	Gestational diabetics	Decreased insulin levels and insulin resistance. Increased insulin sensitivity	[189]

[1] polycystic ovary syndrome; [2] fasting blood sugar.

3. Conclusions

Probiotics and synbiotics have been widely used for the treatment of several conditions and diseases [54,155,186,190–192]. The potentially healing properties of natural products are presented more often in recent years and people tend to turn to more natural ways of treating symptoms or even aiming towards them providing a reversing effect. On the other hand, endocrinology is a very complex area of study. Although hirsutism, a disorder characterised of excess terminal hair in a male-like pattern [88,193], has been generally studied, not much research was conducted on the effects of probiotics/synbiotics on this condition. The complexity of the disorder is also shown through its relationship with lipid metabolism [194]. Main markers for the determination of lipid metabolism, such as low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides are shown to be altered in women suffering from PCOS and other related disorders [195]. Elevated levels of triglycerides and lower levels of LDL, a group of lipoproteins that are the main source of cholesterol, are observed in hirsute women. Moreover, insulin is known to increase the activity of tissue lipoprotein lipases (LPL), an enzyme that takes part in the metabolism of lipoproteins and is regulated by plasma hormones. IR, on the other hand, can lead to the elevation of triglycerides, an observation that indicates an indirect relationship of hirsutism with high levels of lipids through the increase of IR through the elevated levels of androgens and vice versa. However, this complex connection between hormones and lipids appears to be independent, as shown in a study where hirsute women were treated with GnRH and, despite the unaffected IR and lipid metabolism of the subjects, estrogens and androgens were decreased [195]. The vicious circle between increased androgens and IR, as shown in Figure 3, supports the hypothesis that hirsutism can affect the metabolic process of lipoproteins and the related enzymes, through the enhancements of IR. Therefore, treatments that provide an overall improvement to IR and steroid levels could potentially alter the metabolic process of lipids and enzymes. Although there is an extensive research on the effects of androgens on cardiovascular disease risk on men [196–199], not many studies exist on the effects of hirsutism on lipid metabolism. There is a mixed association between the effects of elevated androgen levels on women and their independent relationship with lipids and cardiovascular disease [200]. The purpose of the current study was to investigate the role of probiotics and synbiotics on hirsutism.

The limited literature found on this topic, shows that probiotics can decrease the production of androgens, and specifically total testosterone, and improve m-FG scoring on hirsute women, increasing the levels of SHBG that bind and regulate free testosterone [102,153,201]. Moreover, synbiotics are shown to have a similar effect with probiotics but more enhanced [27].

Therefore, it is suggested that a combination of probiotics and prebiotics can improve and help on the management of hirsutism and other conditions. Additionally, considering the direct relationship of hirsutism with IR [91,95,96,174], the effects of the beneficial compounds on IR was also examined. Growing literature shows a reduction of FBS, insulin levels, insulin resistance and insulin sensitivity after treatments with probiotics and/or synbiotics supports the beneficial effects on hirsutism through the mentioned mechanisms [178–180,202]. Taken together, these findings suggest a role for probiotics and synbiotics in reducing androgens and decreasing m-FG scores, directly and through managing and decreasing IR. Moreover, treatments with probiotics and/or synbiotics are shown to improve the lipid metabolism in hirsute women, reducing serum triglycerides levels [27,167,203], reducing levels of LDL and increasing HDL [27,186,203], although it is not clear whether hirsutism is independently correlated with lipoprotein elevation. The majority of studies found in the literature refer to research conducted on PCOS women, since most hirsute women also suffer from this metabolic syndrome. Current drug therapies on hirsutism including insulin sensitisers, anti-androgen monotherapies and OCPs, can have severe side effects [98,112–114] and a potential therapeutic role of probiotics along with prebiotics, can be a significant relief for women suffering from the disorder.

The effect of the studied microorganisms on the metabolic profile of women is shown to be significant and interestingly, correlated with many abnormalities. The combinational effect of them on IR, steroids and lipids profiles, shows a multifunctional character of these treatments that could potentially support the metabolic processes to such degree that conventional treatments with drugs could be replaced, especially when combined with lifestyle changes, such as exercise and diet. Although there is evidence for the beneficial role of probiotics and synbiotics on hirsutism and the related disorders, more studies need to be conducted on their direct effects, mechanisms, length of treatment and dosage.

Author Contributions: The author confirms sole responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

Funding: This research received no external funding.

Acknowledgments: The author wishes to thank Sotiris Kyriakou for his support.

Conflicts of Interest: The author declares no conflict of interest and there has been no financial support for this work that could have influenced its outcome.

References

1. McGovern, P.E.; Zhang, J.; Tang, J.; Zhang, Z.; Hall, G.R.; Moreau, R.A.; Nunez, A.; Butrym, E.D.; Richards, M.P.; Wang, C.-S.; et al. Fermented beverages of pre- and proto-historic China. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 17593–17598. [CrossRef] [PubMed]
2. Sicard, D.; Legras, J.L. Bread, beer and wine: Yeast domestication in the Saccharomyces sensu stricto complex. *Comptes Rendus -Biol.* **2011**, *334*, 229–236. [CrossRef] [PubMed]
3. Ozen, M.; Dinleyici, E.C. The history of probiotics: The untold story. *Benef. Microbes* **2015**, *6*, 159–165. [CrossRef] [PubMed]
4. Isolauri, E. Probiotics in human disease. *Am. J. Clin. Nutr.* **2001**, *73*, 1142S–1146S. [CrossRef] [PubMed]
5. Vandenplas, Y.; Zakharova, I.; Dmitrieva, Y. Oligosaccharides in infant formula: More evidence to validate the role of prebiotics. *Br. J. Nutr.* **2015**, *113*, 1339–1344. [CrossRef] [PubMed]
6. Gordon, S. Elie Metchnikoff: Father of natural immunity. *Eur. J. Immunol.* **2008**, *38*, 3257–3264. [CrossRef] [PubMed]
7. Rodrigues, K.L.; Gaudino Caputo, L.R.; Tavares Carvalho, J.C.; Evangelista, J.; Schneedorf, J.M. Antimicrobial and healing activity of kefir and kefiran extract. *Int. J. Antimicrob. Agents* **2005**, *25*, 404–408. [CrossRef]
8. Rahimzadeh, G.; Fazeli, M.R.; Mozafari, A.N.; Mesbahi, M. Evaluation of Anti-Microbial Activity and Wound Healing of Kefir | International Journal of Pharmaceutical Sciences and Research. Available online: http://ijpsr.com/bft-article/evaluation-of-anti-microbial-activity-and-wound-healing-of-kefir/?view=fulltext (accessed on 26 November 2018).
9. Atalan, G.; Demirkan, I.; Yaman, H.; Cina, M. Effect of topical kefir application on open wound healing on in vivo study. *Kafkas Univ. Vet. Fak. Dderg.* **2003**, *9*, 43–47.
10. Lolou, V.; Panayiotidis, M.I. Functional role of probiotics and prebiotics on skin health and disease. *Fermentation* **2019**, *5*, 41. [CrossRef]
11. Sharifi, M.; Moridnia, A.; Mortazavi, D.; Salehi, M.; Bagheri, M.; Sheikhi, A. Kefir: A powerful probiotics with anticancer properties. *Med. Oncol.* **2017**, *34*, 183. [CrossRef]
12. Chen, M.J.; Liu, J.R.; Sheu, J.F.; Lin, C.W.; Chuang, C.L. Study on skin care properties of milk kefir whey. *Asian-Australasian J. Anim. Sci.* **2006**, *19*, 905–908. [CrossRef]

13. Collins, M.D.; Phillips, B.A.; Paolo, Z. Deozyribonucleic acid homology studies of lactobacillus casei etc. Collins 1989. *Int. J. Syst. Bacteriol.* **1989**, *39*, 105–108. [CrossRef]
14. Report of a Joint FAO/WHO Working Group on Drafting Guidelines for the Evaluation of Probiotics in Food. Guidelines for the Evaluation of Probiotics in Food. 2002. Available online: https://www.who.int/foodsafety/fs_management/en/probiotic_guidelines.pdf (accessed on 11 January 2021).
15. Goldin, B.R.; Swenson, L.; Dwyer, J.; Sexton, M.; Gorbach, S.L. Effect of diet and Lactobacillus acidophilus supplements on human fecal bacterial enzymes. *J. Natl. Cancer Inst.* **1980**, *64*, 255–261. [CrossRef] [PubMed]
16. Scholz-Ahrens, K.E.; Adolphi, B.; Rochat, F.; Barclay, D.V.; de Vrese, M.; Açil, Y.; Schrezenmeir, J. Effects of probiotics, prebiotics, and synbiotics on mineral metabolism in ovariectomized rats - impact of bacterial mass, intestinal absorptive area and reduction of bone turn-over. *NFS J.* **2016**, *3*, 41–50. [CrossRef]
17. Milani, C.; Duranti, S.; Bottacini, F.; Casey, E.; Turroni, F.; Mahony, J.; Belzer, C.; Delgado Palacio, S.; Arboleya Montes, S.; Mancabelli, L.; et al. The First Microbial Colonizers of the Human Gut: Composition, Activities, and Health Implications of the Infant Gut Microbiota. *Microbiol. Mol. Biol. Rev.* **2017**, *81*, 1–67. [CrossRef]
18. Talebi, S.; Karimifar, M.; Heidari, Z.; Mohammadi, H.; Askari, G. The effects of synbiotic supplementation on thyroid function and inflammation in hypothyroid patients: A randomized, double-blind, placebo-controlled trial. *Complement. Ther. Med.* **2020**, *48*. [CrossRef]
19. Nasri, K.; Jamilian, M.; Rahmani, E.; Bahmani, F.; Tajabadi-Ebrahimi, M.; Asemi, Z. The effects of synbiotic supplementation on hormonal status, biomarkers of inflammation and oxidative stress in subjects with polycystic ovaryfile:///C:/Users/Vassoula/Downloads/29664663.nbib syndrome: A randomized, double-blind, placebo-controlled trial. *BMC Endocr. Disord.* **2018**, *18*, 1–8. [CrossRef]
20. He, M.; Gao, J.; Wu, J.; Zhou, Y.; Fu, H.; Ke, S.; Yang, H.; Chen, C.; Huang, L. Host gender and androgen levels regulate gut bacterial taxa in pigs leading to sex-biased serum metabolite profiles. *Front. Microbiol.* **2019**, *10*, 1–13. [CrossRef]
21. Yarak, S.; Brasil Parada, M.O.A.; Bagatin, E.; Talarico Filho, S.; Hassun, K.M. Hyperandrogenism and skin: Polycystic ovary syndrome and peripheral insulin resistance. *An. Bras. Dermatol.* **2005**, *80*, 395–410. [CrossRef]
22. Carnevali, O.; Avella, M.A.; Gioacchini, G. Effects of probiotic administration on zebrafish development and reproduction. *Gen. Comp. Endocrinol.* **2012**, *188*, 297–302. [CrossRef]
23. Sonal Sekhar, M.; Unnikrishnan, M.K.; Vijayanarayana, K.; Rodrigues, G.S.; Mukhopadhyay, C. Topical application/formulation of probiotics: Will it be a novel treatment approach for diabetic foot ulcer? *Med. Hypotheses* **2014**, *82*, 86–88. [CrossRef] [PubMed]
24. Sikorska, H.; Smoragiewicz, W. Role of probiotics in the prevention and treatment of meticillin-resistant Staphylococcus aureus infections. *Int. J. Antimicrob. Agents* **2013**, *42*, 475–481. [CrossRef] [PubMed]
25. Eggers, S.; Barker, A.; Valentine, S.; Hess, T.; Duster, M.; Safdar, N. Impact of Probiotics for Reducing Infections in Veterans (IMPROVE): Study protocol for a double-blind, randomized controlled trial to reduce carriage of Staphylococcus aureus. *Contemp. Clin. Trials* **2017**, *52*, 39–45. [CrossRef] [PubMed]
26. Frei, R.; Akdis, M.; O'mahony, L. Prebiotics, probiotics, synbiotics, and the immune system: Experimental data and clinical evidence. *Curr. Opin. Gastroenterol.* **2015**, *31*, 153–158. [CrossRef]
27. Rajkumar, H.; Kumar, M.; Das, N.; Kumar, S.N.; Challa, H.R.; Nagpal, R. Effect of Probiotic Lactobacillus salivarius UBL S22 and Prebiotic Fructo-oligosaccharid on Serum Lipids, Inflammatory Markers, Insulin Sensitivity, and Gut Bacteria in Healthy Young Volunteers: A Randomized Controlled Single-Blind Pilot Study. *J. Cardiovasc. Pharmacol. Ther.* **2015**, *20*, 289–298. [CrossRef]
28. Cozzolino, M.; Vitagliano, A.; Pellegrini, L.; Chiurazzi, M.; Andriasani, A.; Ambrosini, G.; Garrido, N. Therapy with probiotics and synbiotics for polycystic ovarian syndrome: A systematic review and meta-analysis. *Eur. J. Nutr.* **2020**, *59*, 2841–2856. [CrossRef]
29. Pandey, K.R.; Naik, S.R.; Vakil, B.V. Probiotics, prebiotics and synbiotics–A review. *J. Food Sci. Technol.* **2015**, *52*, 7577–7587. [CrossRef]
30. Azad, M.A.K.; Sarker, M.; Li, T.; Yin, J. Probiotic Species in the Modulation of Gut Microbiota: An Overview. *Biomed Res. Int.* **2018**, *2018*. [CrossRef]
31. Mori, N.; Kano, M.; Masuoka, N.; Konno, T.; Suzuki, Y.; Miyazaki, K.; Ueki, Y. Effect of probiotic and prebiotic fermented milk on skin and intestinal conditions in healthy young female students. *Biosci. Microbiota Food Health* **2016**, *35*, 105–112. [CrossRef]
32. Sánchez, B.; Delgado, S.; Blanco-Míguez, A.; Lourenço, A.; Gueimonde, M.; Margolles, A. Probiotics, gut microbiota, and their influence on host health and disease. *Mol. Nutr. Food Res.* **2017**, *61*, 1–15. [CrossRef]
33. Britti, M.; Roselli, M.; Finamore, A.; Merendino, N.; Mengheri, E. Regulation of immune response at intestinal and peripheral sites by probiotics. *Biologia (Bratisl)* **2006**, *61*, 735–740. [CrossRef]
34. Thomas, C.M.; Versalovic, J. Probiotics-host communication. *Gut Microbes* **2010**, *1*, 148–163. [CrossRef] [PubMed]
35. Bansal, S.; Mangal, M.; Sharma, S.K.; Gupta, R.K. Non-dairy Based Probiotics: A Healthy Treat for Intestine. *Crit. Rev. Food Sci. Nutr.* **2016**, *56*, 1856–1867. [CrossRef] [PubMed]
36. Wang, X.; Farnell, Y.Z.; Peebles, E.D.; Kiess, A.S.; Wamsley, K.G.S.; Zhai, W. Effects of prebiotics, probiotics, and their combination on growth performance, small intestine morphology, and resident Lactobacillus of male broilers. *Poult. Sci.* **2016**, *95*, 1332–1340. [CrossRef] [PubMed]
37. Friedrich, A.D.; Paz, M.L.; Leoni, J.; Maglio, D.H.G. Message in a bottle: Dialog between intestine and skin modulated by probiotics. *Int. J. Mol. Sci.* **2017**, *18*, 1067. [CrossRef] [PubMed]
38. White, J.S.; Hoper, M.; Parks, R.W.; Clements, W.D.B.; Diamond, T.; Bengmark, S. The probiotic bacterium Lactobacillus plantarum species 299 reduces intestinal permeability in experimental biliary obstruction. *Lett. Appl. Microbiol.* **2006**, *42*, 19–23. [CrossRef]

39. Yamada, T.; Nagata, S.; Kondo, S.; Bian, L.; Wang, C.; Asahara, T.; Ohta, T.; Nomoto, K.; Yamashiro, Y. Effect of Continuous Fermented Milk Intake Containing Lactobacillus casei Strain Shirota on Fever in Mass Infectious Gastroenteritis Rest Home Outbreak. *Kansenshogaku Zasshi* **2009**, *83*, 31–35. [CrossRef]
40. Imaoka, A.; Shima, T.; Kato, K.; Mizuno, S.; Uehara, T.; Matsumoto, S.; Setoyana, H.; Hara, T.; Umesaki, Y. Anti-inflammatory activity of probiotic Bifidobacterium: Enhancement of IL-10 production in peripheral blood mononuclear cells from ulcerative colitis patients and inhibition of IL-8 secretion in HT-29 cells. *World J. Gastroenterol.* **2008**, *14*, 2511–2516. [CrossRef]
41. Abdin, A.A.; Saeid, E.M. An experimental study on ulcerative colitis as a potential target for probiotic therapy by Lactobacillus acidophilus with or without "olsalazine". *J. Crohn's Colitis* **2008**, *2*, 296–303. [CrossRef]
42. Amara, A.A.; Shibl, A. Role of Probiotics in health improvement, infection control and disease treatment and management. *Saudi Pharm. J.* **2015**, *23*, 107–114. [CrossRef]
43. Mego, M.; Májek, J.; Končeková, R.; Ebringer, L.; Čierniková, S.; Rauko, P.; Kováč, M.; Trupl, J.; Slezák, P.; Zajac, V. Intramucosal bacteria in colon cancer and their elimination by probiotic strain Enterococcus faecium M-74 with organic selenium. *Folia Microbiol.* **2005**, *50*, 443–447. [CrossRef] [PubMed]
44. Boudeau, J.; Glasser, A.L.; Julien, S.; Colombel, J.F.; Darfeuille-Michaud, A. Inhibitory effect of probiotic Escherichia coli strain Nissle 1917 on adhesion to and invasion of intestinal epithelial cells by adherent-invasive E.coli strains isolated from patients with Crohn's disease. *Aliment. Pharmacol. Ther.* **2003**, *18*, 45–56. [CrossRef] [PubMed]
45. Anukam, K.C.; Hayes, K.; Summers, K.; Reid, G. Probiotic Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14 may help downregulate TNF-alpha, IL-6, IL-8, IL-10 and IL-12 (p70) in the neurogenic bladder of spinal cord injured patient with urinary tract infections: A two-case study. *Adv. Urol.* **2009**, *2009*. [CrossRef] [PubMed]
46. Thirabunyanon, M.; Boonprasom, P.; Niamsup, P. Probiotic potential of lactic acid bacteria isolated from fermented dairy milks on antiproliferation of colon cancer cells. *Biotechnol. Lett.* **2009**, *31*, 571–576. [CrossRef] [PubMed]
47. Hacini-Rachinel, F.; Gheit, H.; Le Luduec, J.B.; Dif, F.; Nancey, S.; Kaiserlian, D. Oral probiotic control skin inflammation by acting on both effector and regulatory T cells. *PLoS ONE* **2009**, *4*, e4903. [CrossRef] [PubMed]
48. Chapat, L.; Chemin, K.; Dubois, B.; Bourdet-Sicard, R.; Kaiserlian, D. Lactobacillus casei reduces CD8+T cell-mediated skin inflammation. *Eur. J. Immunol.* **2004**, *34*, 2520–2528. [CrossRef]
49. Weise, C.; Zhu, Y.; Ernst, D.; Ku, A.A. Oral administration of Escherichia coli Nissle 1917 prevents allergen-induced dermatitis in mice. *Exp. Dermatol.* **2011**, *20*, 805–809. [CrossRef]
50. Vaiserman, A.M.; Koliada, A.K.; Marotta, F. Gut microbiota: A player in aging and a target for anti-aging intervention. *Ageing Res. Rev.* **2017**, *35*, 36–45. [CrossRef]
51. Musthaq, S.; Mazuy, A.; Jakus, J. The microbiome in dermatology. *Clin. Dermatol.* **2018**, *36*, 390–398. [CrossRef]
52. Kalliomäki, M.; Salminen, S.; Poussa, T.; Isolauri, E. *Probiotics during the First 7 Years of Life: A Cumulative Risk Reduction of Eczema in a Randomized, Placebo-Controlled Trial*; Mosby: Maryland Heights, MI, USA, 2007; Volume 119.
53. Huseini, H.F.; Rahimzadeh, G.; Fazeli, M.R.; Mehrazma, M.; Salehi, M. Evaluation of wound healing activities of kefir products. *Burns* **2012**, *38*, 719–723. [CrossRef]
54. Nasrabadi, H. Study of cutaneous wound healing in rats treated with Lactobacillus plantarum on days 1, 3, 7, 14 and 21. *Afr. J. Pharm. Pharmacol.* **2011**, *5*, 2395–2401. [CrossRef]
55. Jebur, M.S. Therapeutic efficacy of Lactobacillus acidophilus against bacterial isolates from burn wounds. *N. Am. J. Med. Sci.* **2010**, *2*, 586–591. [CrossRef] [PubMed]
56. Tsiouris, C.G.; Tsiouri, M.G. Human microflora, probiotics and wound healing. *Wound Med.* **2017**, *19*, 33–38. [CrossRef]
57. Rumbaugh, K.P.; Griswold, J.A.; Iglewski, B.H.; Hamood, A.N. Contribution of quorum sensing to the virulence of Pseudomonas aeruginosa in burn wound infections. *Infect. Immun.* **1999**, *67*, 5854–5862. [CrossRef] [PubMed]
58. de Oliveira, G.L.V.; Leite, A.Z.; Higuchi, B.S.; Gonzaga, M.I.; Mariano, V.S. Intestinal dysbiosis and probiotic applications in autoimmune diseases. *Immunology* **2017**, *152*, 1–12. [CrossRef]
59. Candon, S.; Perez-Arroyo, A.; Marquet, C.; Valette, F.; Foray, A.P.; Pelletier, B.; Milani, C.; Ventura, M.; Bach, J.F.; Chatenoud, L. Antibiotics in early life alter the gut microbiome and increase disease incidence in a spontaneous mouse model of autoimmune insulin-dependent diabetes. *PLoS ONE* **2015**, *10*, e0125448. [CrossRef]
60. Hickson, M.; D'Souza, A.L.; Muthu, N.; Rogers, T.R.; Want, S.; Rajkumar, C.; Bulpitt, C.J. Use of probiotic Lactobacillus preparation to prevent diarrhoea associated with antibiotics: Randomised double blind placebo controlled trial. *Br. Med. J.* **2007**, *335*, 80–83. [CrossRef]
61. He, C.; Cheng, D.; Peng, C.; Li, Y.; Zhu, Y.; Lu, N. High-fat diet induces dysbiosis of gastric microbiota prior to gut microbiota in association with metabolic disorders in mice. *Front. Microbiol.* **2018**, *9*, 1–9. [CrossRef]
62. Ravussin, Y.; Koren, O.; Spor, A.; Leduc, C.; Gutman, R.; Stombaugh, J.; Knight, R.; Ley, R.E.; Leibel, R.L. Responses of gut microbiota to diet composition and weight loss in lean and obese mice. *Obesity* **2012**, *20*, 738–747. [CrossRef]
63. Ochoa-Repáraz, J.; Kasper, L.H. The Second Brain: Is the Gut Microbiota a Link Between Obesity and Central Nervous System Disorders? *Curr. Obes. Rep.* **2016**, *5*, 51–64. [CrossRef]
64. Calvani, R.; Picca, A.; Lo Monaco, M.R.; Landi, F.; Bernabei, R.; Marzetti, E. Of microbes and minds: A narrative review on the second brain aging. *Front. Med.* **2018**, *5*, 1–11. [CrossRef]
65. Sokol, H.; Seksik, P.; Furet, J.P.; Firmesse, O.; Nion-Larmurier, I.; Beaugerie, L.; Cosnes, J.; Corthier, G.; Marteau, P.; Doraé, J. Low counts of faecalibacterium prausnitzii in colitis microbiota. *Inflamm. Bowel Dis.* **2009**, *15*, 1183–1189. [CrossRef] [PubMed]

66. Sokol, H.; Pigneur, B.; Watterlot, L.; Lakhdari, O.; Bermudez-Humaran, L.G.; Gratadoux, J.-J.; Blugeon, S.; Bridonneau, C.; Furet, J.-P.; Corthier, G.; et al. Faecalibacterium prausnitzii is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. *J. Pathol.* **1990**, *162*, 323–327. [CrossRef] [PubMed]
67. Partlow, J.; Blikslager, A.; Matthews, C.; Law, M.; Daniels, J.; Baker, R.; Labens, R. Effect of topically applied Saccharomyces boulardii on the healing of acute porcine wounds: A preliminary study. *BMC Res. Notes* **2016**, *9*. [CrossRef] [PubMed]
68. Brouwer, M.L.; Wolt-Plompen, S.A.A.; Dubios, A.E.J.; Van Der Heide, S.; Jansen, D.F.; Hoijer, M.A.; Kauffman, H.F.; Duiverman, E.J. No effects of probiotics on atopic dermatitis in infancy: A randomized placebo-controlled trial. *Clin. Exp. Allergy* **2006**, *36*, 899–906. [CrossRef] [PubMed]
69. Sugimoto, S.; Ishii, Y.; Izawa, N.; Masuoka, N.; Kano, M.; Sone, T.; Chiba, K.; Miyazaki, K.; Ishikawa, F. Photoprotective effects of Bifidobacterium breve supplementation against skin damage induced by ultraviolet irradiation in hairless mice. *Photodermatol. Photoimmunol. Photomed.* **2012**, *28*, 312–319. [CrossRef]
70. Queipo-Ortuño, M.I.; Seoane, L.M.; Murri, M.; Pardo, M.; Gomez-Zumaquero, J.M.; Cardona, F.; Casanueva, F.; Tinahones, F.J. Gut Microbiota Composition in Male Rat Models under Different Nutritional Status and Physical Activity and Its Association with Serum Leptin and Ghrelin Levels. *PLoS ONE* **2013**, *8*. [CrossRef]
71. Naruszewicz, M.; Johansson, M.L.; Zapolska-Downar, D.; Bukowska, H. Effect of Lactobacillus plantarum 299v on cardiovascular disease risk factors in smokers. *Am. J. Clin. Nutr.* **2002**, *76*, 1249–1255. [CrossRef]
72. Messaoudi, M.; Lalonde, R.; Violle, N.; Javelot, H.; Desor, D.; Nejdi, A.; Bisson, J.F.; Rougeot, C.; Pichelin, M.; Cazaubiel, M.; et al. Assessment of psychotropic-like properties of a probiotic formulation (Lactobacillus helveticus R0052 and Bifidobacterium longum R0175) in rats and human subjects. *Br. J. Nutr.* **2011**, *105*, 755–764. [CrossRef]
73. Karlsson, F.H.; Tremaroli, V.; Nookaew, I.; Bergström, G.; Behre, C.J.; Fagerberg, B.; Nielsen, J.; Bäckhed, F. Gut metagenome in European women with normal, impaired and diabetic glucose control. *Nature* **2013**, *498*, 99–103. [CrossRef]
74. Vrieze, A.; Van Nood, E.; Holleman, F.; Salojärvi, J.; Kootte, R.S.; Bartelsman, J.F.W.M.; Dallinga-Thie, G.M.; Ackermans, M.T.; Serlie, M.J.; Oozeer, R.; et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. *Gastroenterology* **2012**, *143*, 913–916. [CrossRef] [PubMed]
75. Adlercreutz, H.; Pulkkinen, M.O.; Hämäläinen, E.K.; Korpela, J.T. Studies on the role of intestinal bacteria in metabolism of synthetic and natural steroid hormones. *J. Steroid Biochem.* **1984**, *20*, 217–229. [CrossRef]
76. Markle, J.G.M.; Frank, D.N.; Mortin-Toth, S.; Robertson, C.E.; Feazel, L.M.; Rolle-Kampczyk, U.; Von Bergen, M.; McCoy, K.D.; Macpherson, A.J.; Danska, J.S. Sex differences in the gut microbiome drive hormone-dependent regulation of autoimmunity. *Science* **2013**, *339*, 1084–1088. [CrossRef] [PubMed]
77. Furrie, E.; Macfarlane, S.; Kennedy, A.; Cummings, J.H.; Walsh, S.V.; O'Neil, D.A.; Macfarlane, G.T. Synbiotic therapy (Bifidobacterium longum/Synergy 1) initiates resolution of inflammation in patients with active ulcerative colitis: A randomised controlled pilot trial. *Gut* **2005**, *54*, 242–249. [CrossRef] [PubMed]
78. Liu, R.; Zhang, C.; Shi, Y.; Zhang, F.; Li, L.; Wang, X.; Ling, Y.; Fu, H.; Dong, W.; Shen, J.; et al. Dysbiosis of gut microbiota associated with clinical parameters in polycystic ovary syndrome. *Front. Microbiol.* **2017**, *8*, 1–12. [CrossRef]
79. Hutkins, R.W.; Krumbeck, J.A.; Bindels, L.B.; Cani, P.D.; Fahey, G.; Goh, Y.J.; Hamaker, B.; Martens, E.C.; Mills, D.A.; Rastal, R.A.; et al. Prebiotics: Why definitions matter. *Curr. Opin. Biotechnol.* **2016**, *37*, 1–7. [CrossRef]
80. Valenlia, K.B.; Morshedi, M.; Saghafi-Asl, M.; Shahabi, P.; Abbasi, M.M. Beneficial impacts of Lactobacillus plantarum and inulin on hypothalamic levels of insulin, leptin, and oxidative markers in diabetic rats. *J. Funct. Foods* **2018**, *46*, 529–537. [CrossRef]
81. Jiang, S.; Mohammed, A.A.; Jacobs, J.A.; Cramer, T.A.; Cheng, H.W. Effect of synbiotics on thyroid hormones, intestinal histomorphology, and heat shock protein 70 expression in broiler chickens reared under cyclic heat stress. *Poult. Sci.* **2020**, *99*, 142–150. [CrossRef]
82. Mofidi, F.; Poustchi, H.; Yari, Z.; Nourinayyer, B.; Merat, S.; Sharafkhah, M.; Malekzadeh, R.; Hekmatdoost, A. Synbiotic supplementation in lean patients with non-alcoholic fatty liver disease: A pilot, randomised, double-blind, placebo-controlled, clinical trial. *Br. J. Nutr.* **2017**, *117*, 662–668. [CrossRef]
83. Eslamparast, T.; Poustchi, H.; Zamani, F.; Sharafkhah, M.; Malekzadeh, R.; Hekmatdoost, A. Synbiotic supplementation in nonalcoholic fatty liver disease: A randomized, double-blind, placebo-controlled pilot study. *Am. J. Clin. Nutr.* **2014**, *99*, 535–542. [CrossRef]
84. Steed, H.; MacFarlane, G.T.; Blackett, K.L.; Bahrami, B.; Reynolds, N.; Walsh, S.V.; Cummings, J.H.; MacFarlane, S. Clinical trial: The microbiological and immunological effects of synbiotic consumption—A randomized double-blind placebo-controlled study in active Crohn's disease. *Aliment. Pharmacol. Ther.* **2010**, *32*, 872–883. [CrossRef] [PubMed]
85. Sivamaruthi, B.S. A comprehensive review on clinical outcome of probiotic and synbiotic therapy for inflammatory bowel diseases. *Asian Pac. J. Trop. Biomed.* **2018**, *8*, 179–186. [CrossRef]
86. Westfall, S.; Lomis, N.; Prakash, S. A novel synbiotic delays Alzheimer's disease onset via combinatorial gut-brain-axis signaling in Drosophila melanogaster. *PLoS ONE* **2019**, *14*, e0214985. [CrossRef] [PubMed]
87. Ishikawa, H.; Matsumoto, S.; Ohashi, Y.; Imaoka, A.; Setoyama, H.; Umesaki, Y.; Tanaka, R.; Otani, T. Beneficial effects of probiotic Bifidobacterium and galacto-oligosaccharide in patients with ulcerative colitis: A randomized controlled study. *Digestion* **2011**, *84*, 128–133. [CrossRef] [PubMed]
88. Hatch, R.; Rosenfield, R.L.; Kim, M.H.; Tredway, D. Hirsutism: Implications, etiology, and management. *Am. J. Obstet. Gynecol.* **1981**, *140*, 815–830. [CrossRef]
89. Carmina, E. Prevalence of idiopathic hirsutism. *Eur. J. Endocrinol.* **1998**, *139*, 421–423. [CrossRef]

90. Azziz, R. The evaluation and management of hirsutism. *Obstet. Gynecol.* **2003**, *101*, 995–1007.
91. Archer, J.S.; Chang, R.J. Hirsutism and acne in polycystic ovary syndrome. *Best Pract. Res. Clin. Obstet. Gynaecol.* **2004**, *18*, 737–754. [CrossRef]
92. Franks, S. Diagnosis of polycystic ovarian syndrome: In defense of the Rotterdam criteria. *J. Clin. Endocrinol. Metab.* **2006**, *91*, 786–789. [CrossRef]
93. Calvo, R.M.; Asunción, M.; Sancho, J.; San Millán, J.L.; Escobar-Morreale, H.F. The role of the CAG repeat polymorphism in the androgen receptor gene and of skewed X-chromosome inactivation, in the pathogenesis of hirsutism. *J. Clin. Endocrinol. Metab.* **2000**, *85*, 1735–1740. [CrossRef]
94. Vottero, A.; Stratakis, C.A.; Ghizzoni, L.; Longui, C.A.; Karl, M.; Chrousos, G.P. Androgen receptor-mediated hypersensitivity to androgens in women with nonhyperandrogenic hirsutism: Skewing of X-chromosome inactivation. *J. Clin. Endocrinol. Metab.* **1999**, *84*, 1091–1095. [CrossRef]
95. Ünlühizarci, K.; Karababa, Y.; Bayram, F.; Kelestimur, F. The investigation of insulin resistance in patients with idiopathic hirsutism. *J. Clin. Endocrinol. Metab.* **2004**, *89*, 2741–2744. [CrossRef] [PubMed]
96. Talaei, A.; Adgi, Z.; Mohamadi Kelishadi, M. Idiopathic hirsutism and insulin resistance. *Int. J. Endocrinol.* **2013**, *2013*. [CrossRef]
97. Barbieri, R.L.; Smith, S.; Ryan, K.J. The role of hyperinsulinemia in the pathogenesis of ovarian hyperandrogenism. *Fertil. Steril.* **1988**, *50*, 197–212. [CrossRef] [PubMed]
98. Barrionuevo, P.; Nabhan, M.; Altayar, O.; Wang, Z.; Erwin, P.J.; Asi, N.; Martin, K.A.; Hassan Murad, M. Treatment Options for Hirsutism: A Systematic Review and Network Meta-Analysis. *J. Clin. Endocrinol. Metab.* **2018**, *103*, 1258–1264. [CrossRef] [PubMed]
99. Moghetti, P.; Tosi, F.; Castello, R.; Magnani, C.M.; Negri, C.; Brun, E.; Furlani, L.; Caputo, M.; Muggeo, M. The insulin resistance in women with hyperandrogenism is partially reversed by antiandrogen treatment: Evidence that androgens impair insulin action in women. *J. Clin. Endocrinol. Metab.* **1996**, *81*, 952–960. [CrossRef]
100. Corbould, A. Chronic testosterone treatment induces selective insulin resistance in subcutaneous adipocytes of women. *J. Endocrinol.* **2007**, *192*, 585–594. [CrossRef]
101. Smith, S.; Ravnikar, V.A.; Barbieri, R.L. Androgen and insulin response to an oral glucose challenge in hyperandrogenic women. *Fertil. Steril.* **1987**, *48*, 72–77. [CrossRef]
102. Mathur, R.S.; Moody, L.O.; Landgrebe, S.; Williamson, H.O. Plasma androgens and sex hormone-binding globulin in the evaluation of hirsute females. *Fertil. Steril.* **1981**, *35*, 29–35. [CrossRef]
103. Dunaif, A.; Green, G.; Phelps, R.G.; Lebwohl, M.; Futterweit, W.; Lewy, L. Acanthosis Nigricans, Insulin Action, and Hyperandrogenism: Clinical, Histological, and Biochemical Findings*. *J. Clin. Endocrinol. Metab.* **1991**, *73*, 590–595. [CrossRef]
104. Dunaif, A.; Graf, M.; Mandeli, J.; Laumas, V.; Dobrjansky, A. Characterization of groups of hyperaiidrogenic women with acanthosis nigricans, impaired glucose tolerance, and/or hyperinsulinemia. *J. Clin. Endocrinol. Metab.* **1987**, *65*, 499–507. [CrossRef]
105. Azziz, R.; Carmina, E.; Sawaya, M.E. Idiopathic Hirsutism*. *Endocr. Rev.* **2000**, *21*, 347–362. [CrossRef] [PubMed]
106. Escobar-Morreale, H.F.; Carmina, E.; Dewailly, D.; Gambineri, A.; Kelestimur, F.; Moghetti, P.; Pugeat, M.; Qiao, J.; Wijeyaratne, C.N.; Witchel, S.F.; et al. Epidemiology, diagnosis and management of hirsutism: A consensus statement by the androgen excess and polycystic ovary syndrome society. *Hum. Reprod. Update* **2012**, *18*, 146–170. [CrossRef] [PubMed]
107. Irons, E.E. The clinical evaluation of drugs. *J. Am. Med. Assoc.* **1929**, *93*, 1523–1524. [CrossRef]
108. Ibáñez, L.; de Zegher, F. Low-dose flutamide-metformin therapy for hyperinsulinemic hyperandrogenism in non-obese adolescents and women. *Hum. Reprod. Update* **2006**, *12*, 243–252. [CrossRef] [PubMed]
109. Ibáñez, L.; De Zegher, F. Low-dose combination of flutamide, metformin and an oral contraceptive for non-obese, young women with polycystic ovary syndrome. *Hum. Reprod.* **2003**, *18*, 57–60. [CrossRef]
110. Rautio, K.; Tapanainen, J.S.; Ruokonen, A.; Morin-Papunen, L.C. Effects of metformin and ethinyl estradiol-cyproterone acetate on lipid levels in obese and non-obese women with polycystic ovary syndrome. *Eur. J. Endocrinol.* **2005**, *152*, 269–275. [CrossRef] [PubMed]
111. Ibáñez, L.; De Zegher, F. Ethinylestradiol-drospirenone, flutamide-metformin, or both for adolescents and women with hyperinsulinemic hyperandrogenism: Opposite effects on adipocytokines and body adiposity. *J. Clin. Endocrinol. Metab.* **2004**, *89*, 1592–1597. [CrossRef]
112. Harborne, L.; Fleming, R.; Lyall, H.; Sattar, N.; Norman, J. Metformin or antiandrogen in the treatment of hirsutism in polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* **2003**, *88*, 4116–4123. [CrossRef]
113. Diamanti-Kandarakis, E.; Kouli, C.; Tsianateli, T.; Bergiele, A. Therapeutic effects of metformin on insulin resistance and hyperandrogenism in polycystic ovary syndrome. *Eur. J. Endocrinol.* **1998**, *138*, 269–274. [CrossRef]
114. Haas, J.; Bentov, Y. Should metformin be included in fertility treatment of PCOS patients? *Med. Hypotheses* **2017**, *100*, 54–58. [CrossRef] [PubMed]
115. Dewis, P.; Petsos, P.; Newman, M.; Anderson, D.C. the Treatment of Hirsutism With a Combination of Desogestrel and Ethinyl Oestradiol. *Clin. Endocrinol.* **1985**, *22*, 29–36. [CrossRef] [PubMed]
116. Mastorakos, G.; Koliopoulos, C.; Creatsas, G. Androgen and lipid profiles in adolescents with polycystic ovary syndrome who were treated with two forms of combined oral contraceptives. *Fertil. Steril.* **2002**, *77*, 919–927. [CrossRef]
117. Zeng, X.; Xie, Y.J.; Liu, Y.T.; Long, S.L.; Mo, Z. cheng Polycystic ovarian syndrome: Correlation between hyperandrogenism, insulin resistance and obesity. *Clin. Chim. Acta* **2020**, *502*, 214–221. [CrossRef] [PubMed]

118. Acbay, O.; Gundogdu, S. Can metformin reduce insulin resistance in polycystic ovary syndrome? *Fertil. Steril.* **1996**, *65*, 946–949. [CrossRef]
119. Moghetti, P.; Castello, R.; Negri, C.; Tosi, F.; Perrone, F.; Caputo, M.; Zanolin, E.; Muggeo, M. Metformin effects on clinical features, endocrine and metabolic profiles, and insulin sensitivity in polycystic ovary syndrome: A randomized, double-blind, placebo-controlled 6-month trial, followed by open, long-term clinical evaluation. *J. Clin. Endocrinol. Metab.* **2000**, *85*, 139–146. [CrossRef]
120. Kolodziejczyk, B.; Duleba, A.J.; Spaczynski, R.Z.; Pawelczyk, L. Metformin therapy decreases hyperandrogenism and hyperinsulinemia in women with polycystic ovary syndrome. *Fertil. Steril.* **2000**, *73*, 1149–1154. [CrossRef]
121. Morin-Papunen, L.C.; Koivunen, R.M.; Ruokonen, A.; Martikainen, H.K. Metformin therapy improves the menstrual pattern with minimal endocrine and metabolic effects in women with polycystic ovary syndrome. *Fertil. Steril.* **1998**, *69*, 691–696. [CrossRef]
122. Ibáñez, L.; De Zegher, F. Flutamide-Metformin Therapy to Reduce Fat Mass in Hyperinsulinemic Ovarian Hyperandrogenism: Effects in Adolescents and in Women on Third-Generation Oral Contraception. *J. Clin. Endocrinol. Metab.* **2003**, *88*, 4720–4724. [CrossRef]
123. Carmina, E. Anti-androgens for the treatment of hirsutism. *Expert Opin. Investig. Drugs* **2002**, *11*, 357–363. [CrossRef]
124. Mowszowicz, I.; Wright, F.; Vincens, M.; Rigaud, C.; Nahoul, K.; Mavier, P.; Guillemant, S.; Kuttenn, F.; Mauvais-Jarvis, P. Androgen metabolism in hirsute patients treated with cyproterone acetate. *J. Steroid Biochem.* **1984**, *20*, 757–761. [CrossRef]
125. Corvol, P.; Michaud, A.; Menard, J.; Freifeld, M.; Mahoudeau, J. Antiandrogenic effect of spirolactones: Mechanism of action. *Endocrinology* **1975**, *97*, 52–58. [CrossRef] [PubMed]
126. Gobinet, J.; Poujol, N.; Sultan, C. Molecular action of androgens. *Mol. Cell. Endocrinol.* **2002**, *198*, 15–24. [CrossRef]
127. Dewhurst, C.J.; Underhill, R.; Goldman, S.; Mansfield, M. the Treatment of Hirsutism With Cyproterone Acetate (an Anti-Androgen). *BJOG An Int. J. Obstet. Gynaecol.* **1977**, *84*, 119–123. [CrossRef] [PubMed]
128. Kuttenn, F.; Rigaud, C.; Wright, F.; Mauvais-Jarvis, P. Treatment of hirsutism by oral cyproterone acetate and percutaneous estradiol. *J. Clin. Endocrinol. Metab.* **1980**, *51*, 1107–1111. [CrossRef]
129. Shapiro, G.; Evron, S. A novel use of spironolactone: Treatment of hirsutism. *J. Clin. Endocrinol. Metab.* **1980**, *51*, 429–432. [CrossRef]
130. Jones, D.B.; Ibraham, I.; Edwards, C.R.W. Hair growth and androgen responses in hirsute women treated with continuous cyproterone acetate and cyclical ethinyl oestradiol. *Acta Endocrinol.* **1987**, *116*, 497–501. [CrossRef]
131. Lobo, R.A.; Shoupe, D.; Serafini, P.; Brinton, D.; Horton, R. The effects of two doses of spironolactone on serum androgens and anagen hair in hirsute women. *Fertil. Steril.* **1985**, *43*, 200–205. [CrossRef]
132. Pittaway, D.E.; Maxson, W.S.; Wentz, A.C. Spironolactone in combination drug therapy for unresponsive hirsutism. *Fertil. Steril.* **1985**, *43*, 878–882. [CrossRef]
133. O'brien, R.C.; Cooper, M.E.; Murray, R.M.L.; Seeman, E.; Thomas, A.K.; Jerums, G. Comparison of sequential cyproterone acetate/estrogen versus spironolactone/oral contraceptive in the treatment of hirsutism. *J. Clin. Endocrinol. Metab.* **1991**, *72*, 1008–1013. [CrossRef]
134. Cusan, L.; Dupont, A.; Gomez, J.L.; Tremblay, R.R.; Labrie, F. Comparison of flutamide and spironolactone in the treatment of hirsutism: A randomized controlled trial. *Fertil. Steril.* **1994**, *61*, 281–287. [CrossRef]
135. Müderris, I.I.; Bayram, F.; Özçelik, B.; Güven, M. New alternative treatment in hirsutism: Bicalutamide 25 mg/day. *Gynecol. Endocrinol.* **2002**, *16*, 63–66. [CrossRef] [PubMed]
136. Moretti, C.; Guccione, L.; Giacinto, P. Di; Simonelli, I.; Exacoustos, C.; Toscano, V.; Motta, C.; De Leo, V.; Petraglia, F.; Lenzi, A. Combined oral contraception and bicalutamide in polycystic ovary syndrome and severe hirsutism: A double-blind randomized controlled trial. *J. Clin. Endocrinol. Metab.* **2018**, *103*, 824–838. [CrossRef] [PubMed]
137. Bahceci, M.; Tuzcu, A.; Canoruc, N.; Tuzun, Y.; Kidir, V.; Aslan, C. Serum C-reactive protein (CRP) levels and insulin resistance in non-obese women with polycystic ovarian syndrome, and effect of bicalutamide on hirsutism, CRP levels and insulin resistance. *Horm. Res.* **2004**, *62*, 283–287. [CrossRef] [PubMed]
138. 138. Goswami, P.K.; Khale, A.; Ogale, S. O. Natural remedies for polycystic ovarian syndrome (PCOS): A review. *Int. J. Pharm. Phytopharm. Res.* **2012**, *1*, 396–402.
139. Kolivand, M.; Keramat, A.; Khosravi, A. The Effect of Herbal Teas on Management of Polycystic Ovary Syndrome: A Systematic Review. *J. Midwifery Reprod. Heal.* **2017**, *5*, 1098–1106. [CrossRef]
140. Akdoğan, M.; Tamer, M.N.; Cüre, E.; Cüre, M.C.; Köroğlu, B.K.; Delibaş, N. Effect of spearmint (Mentha spicata Labiatae) teas on androgen levels in women with hirsutism. *Phyther. Res.* **2007**, *21*, 444–447. [CrossRef]
141. Grant, P.; Ramasamy, S. An update on plant derived anti-androgens. *Int. J. Endocrinol. Metab.* **2012**, *10*, 497–502. [CrossRef]
142. Grant, P. Spearmint Herbal Tea has Signifi cant Anti-androgen Effects in Polycystic Ovarian Syndrome. A Randomized Controlled Trial. *Phyther. Res.* **2010**, *24*, 186–188. [CrossRef]
143. Haj-Husein, I.; Tukan, S.; Alkazaleh, F. The effect of marjoram (Origanum majorana) tea on the hormonal profile of women with polycystic ovary syndrome: A randomised controlled pilot study. *J. Hum. Nutr. Diet.* **2016**, *29*, 105–111. [CrossRef]
144. Phy, J.L.; Pohlmeier, A.M.; Cooper, J.A.; Watkins, P.; Spallholz, J.; Harris, K.S.; Berenson, A.B.; Boylan, M. Low Starch/Low Dairy Diet Results in Successful Treatment of Obesity and Co- Morbidities Linked to Polycystic Ovary Syndrome (PCOS). *J. Obes. Weight Loss Ther.* **2015**, *5*, 1–12. [CrossRef]
145. Pohlmeier, A.M.; Phy, J.L.; Watkins, P.; Boylan, M.; Spallholz, J.; Harris, K.S.; Cooper, J.A. Effect of a low-starch/low-dairy diet on fat oxidation in overweight and obese women with polycystic ovary syndrome. *Appl. Physiol. Nutr. Metab.* **2014**, *39*, 1237–1244. [CrossRef] [PubMed]

146. Janiszewska, J.; Ostrowska, J.; Szostak-Węgierek, D. Milk and Dairy Products and Their Impact on Carbohydrate Metabolism and Fertility-A Potential Role in the Diet of Women with Polycystic Ovary Syndrome. *Nutrients* **2020**, *12*. [CrossRef] [PubMed]
147. Shamasbi, S.G.; Ghanbari-Homayi, S.; Mirghafourvand, M. The effect of probiotics, prebiotics, and synbiotics on hormonal and inflammatory indices in women with polycystic ovary syndrome: A systematic review and meta-analysis. *Eur. J. Nutr.* **2020**, *59*, 433–450. [CrossRef] [PubMed]
148. Tabrizi, R.; Ostadmohammadi, V.; Akbari, M.; Lankarani, K.B.; Vakili, S.; Peymani, P.; Karamali, M.; Kolahdooz, F.; Asemi, Z. The Effects of Probiotic Supplementation on Clinical Symptom, Weight Loss, Glycemic Control, Lipid and Hormonal Profiles, Biomarkers of Inflammation, and Oxidative Stress in Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-analysis of Ra. *Probiotics Antimicrob. Proteins* **2019**. [CrossRef] [PubMed]
149. Ostadmohammadi, V.; Jamilian, M.; Bahmani, F.; Asemi, Z. Vitamin D and probiotic co-supplementation affects mental health, hormonal, inflammatory and oxidative stress parameters in women with polycystic ovary syndrome. *J. Ovarian Res.* **2019**, *12*, 1–8. [CrossRef]
150. Jamilian, M.; Mansury, S.; Bahmani, F.; Heidar, Z.; Amirani, E.; Asemi, Z. The effects of probiotic and selenium co-supplementation on parameters of mental health, hormonal profiles, and biomarkers of inflammation and oxidative stress in women with polycystic ovary syndrome 11 Medical and Health Sciences 1103 Clinical Sciences. *J. Ovarian Res.* **2018**, *11*, 1–7. [CrossRef]
151. He, F.F.; Li, Y.M. Role of gut microbiota in the development of insulin resistance and the mechanism underlying polycystic ovary syndrome: A review. *J. Ovarian Res.* **2020**, *13*, 1–13. [CrossRef]
152. Guevara, G.; Flores, Y.O.; De Las Heras, L.F.; Perera, J.; Navarro Llorens, J.M. Metabolic engineering of Rhodococcus ruber Chol-4: A cell factory for testosterone production. *PLoS ONE* **2019**, *14*. [CrossRef]
153. Colldén, H.; Landin, A.; Wallenius, V.; Elebring, E.; Fändriks, L.; Nilsson, M.E.; Ryberg, H.; Poutanen, M.; Sjögren, K.; Vandenput, L.; et al. The gut microbiota is a major regulator of androgen metabolism in intestinal contents. *Am. J. Physiol. Endocrinol. Metab.* **2019**, *317*, E1182–E1192. [CrossRef]
154. Tremellen, K.; Pearce, K. Dysbiosis of Gut Microbiota (DOGMA)—A novel theory for the development of Polycystic Ovarian Syndrome. *Med. Hypotheses* **2012**, *79*, 104–112. [CrossRef] [PubMed]
155. Lindheim, L.; Bashir, M.; Münzker, J.; Trummer, C.; Zachhuber, V.; Leber, B.; Horvath, A.; Pieber, T.R.; Gorkiewicz, G.; Stadlbauer, V.; et al. Alterations in gut microbiome composition and barrier function are associated with reproductive and metabolic defects in women with polycystic ovary syndrome (PCOS): A pilot study. *PLoS ONE* **2017**, *12*, 1–20. [CrossRef] [PubMed]
156. Guo, Y.; Qi, Y.; Yang, X.; Zhao, L.; Wen, S.; Liu, Y.; Tang, L. Association between polycystic ovary syndrome and gut microbiota. *PLoS ONE* **2016**, *11*, e0153196. [CrossRef] [PubMed]
157. Karamali, M.; Eghbalpour, S.; Rajabi, S.; Jamilian, M.; Bahmani, F.; Tajabadi-Ebrahimi, M.; Keneshlou, F.; Mirhashemi, S.M.; Chamani, M.; Hashem Gelougerdi, S.; et al. Effects of Probiotic Supplementation on Hormonal Profiles, Biomarkers of Inflammation and Oxidative Stress in Women With Polycystic Ovary Syndrome: A Randomized, Double-Blind, Placebo-Controlled Trial. *Arch. Iran. Med.* **2018**, *21*, 1–7. [PubMed]
158. Maktabi, M.; Chamani, M.; Asemi, Z. The Effects of Vitamin D Supplementation on Metabolic Status of Patients with Polycystic Ovary Syndrome: A Randomized, Double-Blind, Placebo-Controlled Trial. *Horm. Metab. Res.* **2017**, *49*, 493–498. [CrossRef]
159. Raja-Khan, N.; Shah, J.; Stetter, C.M.; Lott, M.E.J.; Kunselman, A.R.; Dodson, W.C.; Legro, R.S. High-dose vitamin D supplementation and measures of insulin sensitivity in polycystic ovary syndrome: A randomized, controlled pilot trial. *Fertil. Steril.* **2014**, *101*, 1740–1746. [CrossRef] [PubMed]
160. Xue, Y.; Xu, P.; Xue, K.; Duan, X.; Cao, J.; Luan, T.; Li, Q.; Gu, L. Effect of vitamin D on biochemical parameters in polycystic ovary syndrome women: A meta-analysis. *Arch. Gynecol. Obstet.* **2017**, *295*, 487–496. [CrossRef]
161. Liao, D.; Zhong, C.; Li, C.; Mo, L.; Liu, Y. Meta-analysis of the effects of probiotic supplementation on glycemia, lipidic profiles, weight loss and C-reactive protein in women with polycystic ovarian syndrome. *Minerva Med.* **2018**, *109*, 479–487. [CrossRef]
162. Laganà, A.S.; Vitale, S.G.; Ban Frangež, H.; Vrtačnik-Bokal, E.; D'Anna, R. Vitamin D in human reproduction: The more, the better? An evidence-based critical appraisal. *Eur. Rev. Med. Pharmacol. Sci.* **2017**, *21*, 4243–4251.
163. Monastra, G.; De Grazia, S.; De Luca, L.; Vittorio, S.; Unfer, V. Vitamin D: A steroid hormone with progesterone-like activity. *Eur. Rev. Med. Pharmacol. Sci.* **2018**, *22*, 2502–2512. [CrossRef]
164. Akbari, M.; Ostadmohammadi, V.; Lankarani, K.B.; Tabrizi, R.; Kolahdooz, F.; Heydari, S.T.; Kavari, S.H.; Mirhosseini, N.; Mafi, A.; Dastorani, M.; et al. The Effects of Vitamin D Supplementation on Biomarkers of Inflammation and Oxidative Stress among Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Horm. Metab. Res.* **2018**, *50*, 271–279. [CrossRef] [PubMed]
165. Zhang, F.; Ma, T.; Cui, P.; Tamadon, A.; He, S.; Huo, C.; Yierfulati, G.; Xu, X.; Hu, W.; Li, X.; et al. Diversity of the gut microbiota in dihydrotestosterone-induced PCOS rats and the pharmacologic effects of diane-35, probiotics, and berberine. *Front. Microbiol.* **2019**, *10*, 175. [CrossRef] [PubMed]
166. Kassaian, N.; Feizi, A.; Aminorroaya, A.; Jafari, P.; Ebrahimi, M.T.; Amini, M. The effects of probiotics and synbiotic supplementation on glucose and insulin metabolism in adults with prediabetes: A double-blind randomized clinical trial. *Acta Diabetol.* **2018**, *55*, 1019–1028. [CrossRef] [PubMed]
167. Ahmadi, S.; Jamilian, M.; Karamali, M.; Tajabadi-Ebrahimi, M.; Jafari, P.; Taghizadeh, M.; Memarzadeh, M.R.; Asemi, Z. Probiotic supplementation and the effects on weight loss, glycaemia and lipid profiles in women with polycystic ovary syndrome: A randomized, double-blind, placebo-controlled trial. *Hum. Fertil.* **2017**, *20*, 254–261. [CrossRef] [PubMed]

168. Laitinen, K.; Poussa, T.; Isolauri, E. Probiotics and dietary counselling contribute to glucose regulation during and after pregnancy: A randomised controlled trial. *Br. J. Nutr.* **2009**, *101*, 1679–1687. [CrossRef] [PubMed]
169. Andreasen, A.S.; Larsen, N.; Pedersen-Skovsgaard, T.; Berg, R.M.G.; Mller, K.; Svendsen, K.D.; Jakobsen, M.; Pedersen, B.K. Effects of Lactobacillus acidophilus NCFM on insulin sensitivity and the systemic inflammatory response in human subjects. *Br. J. Nutr.* **2010**, *104*, 1831–1838. [CrossRef] [PubMed]
170. Barreto, F.M.; Colado Simão, A.N.; Morimoto, H.K.; Batisti Lozovoy, M.A.; Dichi, I.; Helena da Silva Miglioranza, L. Beneficial effects of Lactobacillus plantarum on glycemia and homocysteine levels in postmenopausal women with metabolic syndrome. *Nutrition* **2014**, *30*, 939–942. [CrossRef]
171. Kocsis, T.; Molnár, B.; Németh, D.; Hegyi, P.; Szakács, Z.; Bálint, A.; Garami, A.; Soós, A.; Márta, K.; Solymár, M. Probiotics have beneficial metabolic effects in patients with type 2 diabetes mellitus: A meta-analysis of randomized clinical trials. *Sci. Rep.* **2020**, *10*, 1–14. [CrossRef]
172. Ardeshirlarijani, E.; Tabatabaei-Malazy, O.; Mohseni, S.; Qorbani, M.; Larijani, B.; Baradar Jalili, R. Effect of probiotics supplementation on glucose and oxidative stress in type 2 diabetes mellitus: A meta-analysis of randomized trials. *DARU J. Pharm. Sci.* **2019**, *27*, 827–837. [CrossRef]
173. Shoaei, T.; Heidari-Beni, M.; Tehrani, H.G.; Feizi, A.; Esmaillzadeh, A.; Askari, G. Effects of probiotic supplementation on pancreatic β-cell function and c-reactive protein in women with polycystic ovary syndrome: A randomized double-blind placebo-controlled clinical trial. *Int. J. Prev. Med.* **2015**, *6*, 25–30. [CrossRef]
174. Azziz, R. The hyperandrogenic-insulin-resistant acanthosis nigricans syndrome: Therapeutic response. *Fertil. Steril.* **1994**, *61*, 570–572. [CrossRef]
175. Gulan, T.; Yeernuer, T.; Sui, S.; Mayinuer, N. A rat model of maternal polycystic ovary syndrome shows that exposure to androgens in utero results in dysbiosis of the intestinal microbiota and metabolic disorders of the newborn rat. *Med. Sci. Monit.* **2019**, *25*, 9377–9391. [CrossRef]
176. Falcone, T.; Finegood, D.T.; Fantus, I.G.; Morris, D. Androgen response to endogenous insulin secretion during the frequently sampled intravenous glucose tolerance test in normal and hyperandrogenic women. *J. Clin. Endocrinol. Metab.* **1990**, *71*, 1653–1657. [CrossRef] [PubMed]
177. Tosi, F.; Negri, C.; Brun, E.; Castello, R.; Faccini, G.; Bonora, E.; Muggeo, M.; Toscano, V.; Moghetti, P. Insulin enhances ACTH-stimulated androgen and glucocorticoid metabolism in hyperandrogenic women. *Eur. J. Endocrinol.* **2011**, *164*, 197–203. [CrossRef]
178. Esmaeilinezhad, Z.; Babajafari, S.; Sohrabi, Z.; Eskandari, M.H.; Amooee, S.; Barati-Boldaji, R. Effect of synbiotic pomegranate juice on glycemic, sex hormone profile and anthropometric indices in PCOS: A randomized, triple blind, controlled trial. *Nutr. Metab. Cardiovasc. Dis.* **2019**, *29*, 201–208. [CrossRef] [PubMed]
179. Karimi, E.; Moini, A.; Yaseri, M.; Shirzad, N.; Sepidarkish, M.; Hossein-Boroujerdi, M.; Hosseinzadeh-Attar, M.J. Effects of synbiotic supplementation on metabolic parameters and apelin in women with polycystic ovary syndrome: A randomised double-blind placebo-controlled trial. *Br. J. Nutr.* **2018**, *119*, 398–406. [CrossRef] [PubMed]
180. Samimi, M.; Dadkhah, A.; Haddad Kashani, H.; Tajabadi-Ebrahimi, M.; Hosseini, E.S.; Asemi, Z. The effects of Synbiotic Supplementation on Metabolic Status in Women With Polycystic Ovary Syndrome: A Randomized Double-Blind Clinical Trial. *Probiotics Antimicro. Prot.* **2019**, 1355–1361. [CrossRef]
181. Yang, J.; Huang, K.; Qin, S.; Wu, X.; Zhao, Z.; Chen, F. Antibacterial action of selenium-enriched probiotics against pathogenic escherichia coli. *Dig. Dis. Sci.* **2009**, *54*, 246–254. [CrossRef]
182. Nido, S.A.; Shituleni, S.A.; Mengistu, B.M.; Liu, Y.; Khan, A.Z.; Gan, F.; Kumbhar, S.; Huang, K. Effects of Selenium-Enriched Probiotics on Lipid Metabolism, Antioxidative Status, Histopathological Lesions, and Related Gene Expression in Mice Fed a High-Fat Diet. *Biol. Trace Elem. Res.* **2016**, *171*, 399–409. [CrossRef]
183. Molan, A.L. Antioxidant and prebiotic activities of selenium-containing green tea. *Nutrition* **2013**, *29*, 476–477. [CrossRef]
184. Razavi, M.; Jamilian, M.; Kashan, Z.F.; Heidar, Z.; Mohseni, M.; Ghandi, Y.; Bagherian, T.; Asemi, Z. Selenium Supplementation and the Effects on Reproductive Outcomes, Biomarkers of Inflammation, and Oxidative Stress in Women with Polycystic Ovary Syndrome. *Horm. Metab. Res.* **2016**, *48*, 185–190. [CrossRef] [PubMed]
185. Mohammad Hosseinzadeh, F.; Hosseinzadeh-Attar, M.J.; Yekaninejad, M.S.; Rashidi, B. Effects of selenium supplementation on glucose homeostasis and free androgen index in women with polycystic ovary syndrome: A randomized, double blinded, placebo controlled clinical trial. *J. Trace Elem. Med. Biol.* **2016**, *34*, 56–61. [CrossRef] [PubMed]
186. Shabani, A.; Noshadian, M.; Jamilian, M.; Chamani, M.; Mohammadi, S.; Asemi, Z. The effects of a novel combination of selenium and probiotic on weight loss, glycemic control and markers of cardio-metabolic risk in women with polycystic ovary syndrome. *J. Funct. Foods* **2018**, *46*, 329–334. [CrossRef]
187. Faghihi, T.; Radfar, M.; Barmal, M.; Amini, P.; Qorbani, M.; Abdollahi, M.; Larijani, B. A randomized, placebo-controlled trial of selenium supplementation in patients with type 2 diabetes: Effects on glucose homeostasis, oxidative stress, and lipid profile. *Am. J. Ther.* **2014**, *21*, 491–495. [CrossRef]
188. Asemi, Z.; Zare, Z.; Shakeri, H.; Sabihi, S.S.; Esmaillzadeh, A. Effect of multispecies probiotic supplements on metabolic profiles, hs-CRP, and oxidative stress in patients with type 2 diabetes. *Ann. Nutr. Metab.* **2013**, *63*, 1–9. [CrossRef]
189. Ahmadi, S.; Jamilian, M.; Tajabadi-Ebrahimi, M.; Jafari, P.; Asemi, Z. The effects of synbiotic supplementation on markers of insulin metabolism and lipid profiles in gestational diabetes: A randomised, double-blind, placebo-controlled trial. *Br. J. Nutr.* **2016**, *116*, 1394–1401. [CrossRef]

190. Fitzpatrick, L.R.; Small, J.; Hoerr, R.A.; Bostwick, E.F.; Maines, L.; Koltun, W.A. In vitro and in vivo effects of the probiotic Escherichia coli strain M-17: Immunomodulation and attenuation of murine colitis. *Br. J. Nutr.* **2008**, *100*, 530–541. [CrossRef]
191. Farnworth, E.R. Kefir a complex probiotic. *Food Sci. Technol. Bull. Funct. Foods* **2006**, *2*, 1–17. [CrossRef]
192. Serafini, F.; Turroni, F.; Ruas-Madiedo, P.; Lugli, G.A.; Milani, C.; Duranti, S.; Zamboni, N.; Bottacini, F.; van Sinderen, D.; Margolles, A.; et al. Kefir fermented milk and kefiran promote growth of Bifidobacterium bifidum PRL2010 and modulate its gene expression. *Int. J. Food Microbiol.* **2014**, *178*, 50–59. [CrossRef]
193. Sonino, N.; Faval, G.A.; Mani, E.; Belluardo, P.; Boscaro, M. Quality of life of hirsute women. *Postgrad. Med. J.* **1993**, *69*, 186–189. [CrossRef]
194. Wild, R.A. Lipid metabolism and hyperandrogenism. *Clin. Obstet. Gynecol.* **1991**, *34*, 864–871. [CrossRef] [PubMed]
195. Wild, R.A.; Alaupovic, P.; Parker, I.J. Lipid and apolipoprotein abnormalities in hirsute women: I. The association with insulin resistance. *Am. J. Obstet. Gynecol.* **1992**, *166*, 1191–1197. [CrossRef]
196. Laughlin, G.A.; Barrett-Connor, E.; Bergstrom, J. Low serum testosterone and mortality in older men. *J. Clin. Endocrinol. Metab.* **2008**, *93*, 68–75. [CrossRef] [PubMed]
197. Araujo, A.B.; Dixon, J.M.; Suarez, E.A.; Murad, M.H.; Guey, L.T.; Wittert, G.A. Endogenous testosterone and mortality in men: A systematic review and meta-analysis. *J. Clin. Endocrinol. Metab.* **2011**, *96*, 3007–3019. [CrossRef] [PubMed]
198. Corona, G.; Rastrelli, G.; Monami, M.; Guay, A.; Buvat, J.; Sforza, A.; Forti, G.; Mannucci, E.; Maggi, M. Hypogonadism as a risk factor for cardiovascular mortality in men: A meta-analytic study. *Eur. J. Endocrinol.* **2011**, *165*, 687–701. [CrossRef] [PubMed]
199. Ruige, J.B.; Mahmoud, A.M.; De Bacquer, D.; Kaufman, J.M. Endogenous testosterone and cardiovascular disease in healthy men: A meta-analysis. *Heart* **2011**, *97*, 870–875. [CrossRef] [PubMed]
200. Penn, C.A.; Chan, J.; Mesaros, C.; Snyder, N.W.; Rader, D.J.; Sammel, M.D.; Dokras, A. Association of serum androgens and coronary artery calcium scores in women. *Fertil. Steril.* **2019**, *112*, 586–593. [CrossRef]
201. Diamondf, M.P.; Grainger, D.A.; Laudano, A.J.; Starick-Zych, K.; Defronzo, R.A. Effect of acute physiological elevations of insulin on circulating androgen levels in nonobese women. *J. Clin. Endocrinol. Metab.* **1991**, *72*, 883–887. [CrossRef]
202. Kim, Y.A.; Keogh, J.B.; Clifton, P.M. Probiotics, prebiotics, synbiotics and insulin sensitivity. *Nutr. Res. Rev.* **2017**, *31*, 35–51. [CrossRef]
203. Raygan, F.; Ostadmohammadi, V.; Asemi, Z. The effects of probiotic and selenium co-supplementation on mental health parameters and metabolic profiles in type 2 diabetic patients with coronary heart disease: A randomized, double-blind, placebo-controlled trial. *Clin. Nutr.* **2019**, *38*, 1594–1598. [CrossRef]