Short title: Health Benefits of Soybean

Nutritional and Health Benefits of Soybean to Human Immunity

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Abstract

Soybean is one of the most important crops in the world, which is not only adapted to various environmental conditions, but also abundant in crucial nutritional ingredients for human being, such as soy protein, soy isoflavone and several bioactive components. Soy protein might be the most important nutritional component in soybean, because it provides all amino acids and several bioactive peptides for human health, which could lower cholesterol levels and may resist virus infection. Soy isoflavone usually refers as phytoestrogen, which has the functions of resisting breast cancer and relieving menopause syndrome. Soybean oil could reduce the plasma cholesterol, while saponins exhibit the bioactivity of resisting HIV and preventing osteoporosis. As for phytosterol, it has the functions of decreasing blood cholesterol levels and reducing the intestinal absorption of dietary and endogenous cholesterol. Soybean and its derived products have great potential in enhancing human immunity. In a word, soybean, a tiny seed from China, is both of highly nutritional and medical value for human health and immunity, and therefore could protect billions of people in the world.

Key words: Soy protein; soy isoflavone; bioactive components; human health, immunity

Introduction

An old Chinese saying is that "the medicines and foods are homologous", which implies that the foods and medicines are the same things in essence. This statement is typically true for soybean plant (Glycine max L. Merr.), soybean and soy-derived foods play a vital role in human diet and is highly valuable to human health and immunity.

Currently, soybean has been one of the most important crops in the world with the global annual yield of 3.34 hundred million ton, according to the FAOSATA database. There are about 50 countries in the world growing soybean, while the United States, Brazil, Argentina, China and India are the five main soybean production countries. These countries stretch across western and southern hemispheres, and are distributed to different latitude with various climate. Obviously, soybean is a crop which is suited for planting in a wide range of the world, since though the contents of nutritional compounds in soybean seed would be fluctuated with the change of climate, the fluctuation of compounds in soybean is significantly smaller than some other crops (Ortiz *et al.,* 2020). Moreover, based on the diverse environment conditions, soybean germplasm could be domesticated to various cultivars with different features, and therefore the advantages of soybean would be gave full play. For instance, within a range of temperature, the soybean oil content would increase if the temperature rises, while protein content would increase if the temperature drops (Song *et al.,* 2016). Thus, the total production of soy oil and protein might be improved, if the high oil soybean cultivars are planted in high-temperature area while the soybean with high protein contents are cultivated in low-temperature region.

Soybean is the corner stone of East Asian nutrition, and has been permeating into daily diet and cuisine culture worldwide, for it is abundant in crucial nutritional ingredients for human (Fig.1), such as soy protein, soybean oil and soy isoflavone (Zhang *et al.,* 2017; Chen *et al.,* 2021), and easy to process into food products like Tofu (Sui *et al.,* 2021).

Soy protein is the primary source of plant protein for human beings, for the protein content of soybean is significantly higher than that of other crops. Many soy protein-derived foods win our favors, including tofu, soy sauce, soymilk, soyabean-based formula for infants, soybean meal (protein powder) and other meat analogs (Sui *et al.,* 2021). Meanwhile, increasing the ratio of soy proteins in daily diet is of great benefit to human, because: 1) soy protein provides all the essential amino acids and a good balance in amino acid composition; 2) soy protein is abundant in physiologically beneficial components which have been shown to lower the cholesterol level, and reduce the risk of hyperlipidemia and cardiovascular diseases (Nishinari *et al.,* 2014). Soybean peptides have been demonstrated to resist virus infection by generating anti-virus metabolites and inactivating SARS-CoV-2 virus *in vitro* (El-Hawary *et al.,* 2021; Oba *et al.,* 2021). Thus, further understanding and exploiting the properties, functions, nutritional and medical values of soy protein could promote its application in human health and immunity.

Soy isoflavone, a kind of plant secondary metabolite, belongs to a group of 3-phenyl derivative synthesized by cinnamyl-CoA (Ku *et al.,* 2020; Chen *et al.,* 2021). Though compared to soy protein soy isoflavone is relatively lower in soybean seed, it is commonly referred as phytoestrogens. Soy isoflavone could weakly interact with the estrogen receptors of human beings, as well as other mammals, and thus exhibits the estrogen-antagonistic bioactivity (Zhao *et al.,* 2009). Besides, soy isoflavone is valuable for human health, since it has the functions of reducing blood pressure, lowering blood cholesterol, improving the cognitive ability of human brain and relieving menopause syndrome (Durazzo *et al.,* 2019). Consequently, the consumption of soybean as natural sources of isoflavones for human beings, due to its medical value has attracted great attention in clinic application.

Soybean oil, saponins and phytosterol also have greater impacts on human health and immunity. Soybean oil, an important quality trait in soybean, could reduce the plasma cholesterol (Zhang *et al.,* 2017). Saponins could resist HIV and prevent osteoporosis (Elekofehinti *et al.,* 2021), while phytosterol exhibits the bioactivities of decreasing blood cholesterol levels, as well as reducing the intestinal absorption of dietary and endogenous cholesterol (Choi *et al.,* 2007).

This chapter intends to promote the cognition that soybean is beneficial for human health and immunity, by summarizing the properties, nutritional and medical functions of various biological components from soybean plants.

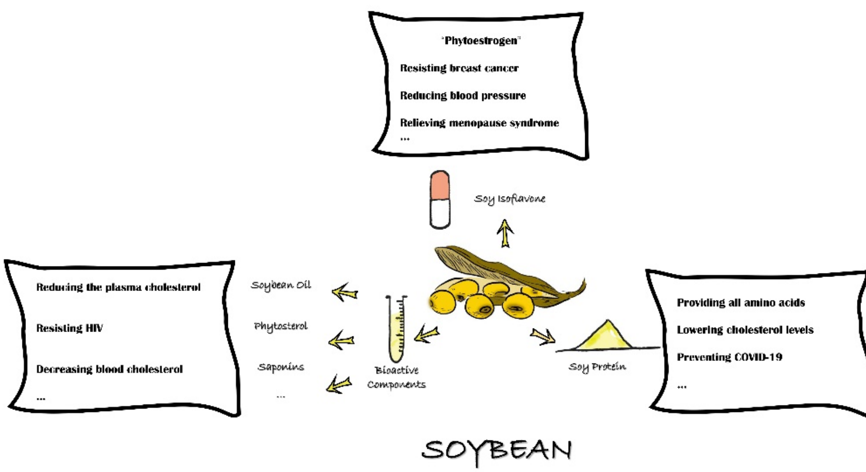

Fig.1: The major soybean compounds and their benefits for human health

Taxonomy

The genus Glycine is divided into two subgenera Glycine (perennials) and Soja (Moench) F. J. Herm (annuals). Plant taxonomists have described 15 additional perennial Glycine, while the Soja includes the cultivated soybean, G. max and G. soja, the wild annual soybean. The path of migration northward from ancestral region to China from a common progenitor is assumed by Singh *et al.,* (2001) as wild perennial (2n=4x=40, unknow or extinct) to wild annual (2n=4x=40; G. soja) to soybean (2n=4x=40; G. max, cultigen). All currently described species of the genus Glycine exhibit diploid-like meiosis, are primarily inbreeders and produce cleistogamous seed.

Origin and distribution

Linguistic, geographical, and historical evidence suggest that soybean emerged as a domesticate during the Zhou dynasty in the eastern half of north China 5000 years ago (Foschia *et al.,* 2017). By the first century A.D., the soybean probably reached central and south China as well as peninsular Korea. The movement of soybean germplasm within the primary gene center is associated with the development and consolidation of territories Sand the degeneration of Chinese dynasties (Ho 1969; Hymowitz 1970). From about the first century A.D., to the Age of Discovery (15^{th}-16^{th} century), soybeans were introduced into several countries with land races eventually developing in Japan, Indonesia, Philippines, Vietnam, and north India. These regions comprise a secondary gene center. Soybean was then introduced to Europe from 17^{th} century and North America in the mid-18^{th}century.

Soy bioactive compounds and their health benefits

Soy protein and its bioactive components: Soy protein might be the most important nutrient for human life. The protein content in soybean is more than 40% (with 13% standard water), while the figure of wheat and rice is only 12% and 10% on average respectively, indicating that soybean is the better protein source for human beings compared with other major crops.

Based on the solubility patterns, soy protein contains two categories: globulins and albumins (Osborne 1908).The albumin is salt-solution soluble. The globulin, a kind of water-soluble protein, is the primary storage protein in soybean. Soy protein could be also separated into four major groups according to precipitation coefficient: 2S, 7S, 11S and 15S (Sugawara *et al.,* 2007). Most of albumins is 2S protein, whereas the globulins can be further divided into 2S (a little), 7S, 11S and 15S group. The 2S, 7S, 11S and 15S protein accounts for 20%, 40%, 30% and 10% of the soybean protein respectively. The2S protein includes most of low-molecular-weight proteins, such as Bowman-Birk trypsin inhibitor and Kunitz trypsin inhibitor, both of which are related to delayed growth in children (Sugawara *et al.,* 2007; Sui *et al.,* 2021).The 7S fraction consists of hemagglutinin, lipoxygenase, β-conglycinin and α-amylase (Puppo and Añón 1998). The 11S protein is formed by the soybean glycinin (Nielsen *et al.,* 1989), while the 15S protein, usually reported to be the polymers, is the storage protein in soybean (Natarajan *et al.,* 2006). Although soy protein contains various components, there are two major constituents: β-conglycinin (7S globulin) and glycinin (11S globulin). The quaternary structures of these two components are different (Adachi *et al.,* 2003), but they contain similar amino acid sequences and might be derived from a common precursor (Adachi *et al.,* 2001). Additionally, the sulfur-containing amino acids are abundant in glycinin, but lower in β-conglycinin. As the β subunit, a major domain of β-conglycinin, is low in methionine and cysteine.

The composition and ratio of amino acids is an important reason for the protein diversity, which is a vital standard to estimate the nutritional value of protein. There are about 20 common amino acids in the biological kingdom, including eight essential amino acids which could not be synthesize in humans (Friedman and Brandon 2001). Soy protein provides all common amino acids for human beings; thus, it is high-quality protein for human beings. In contrast with fat and starch, the body would not synthesize excess amino acids for storage, so the amino acids are required for people every day. Fortunately, the amino acid composition of soy protein is well-balanced for human diet (Natarajan *et al.,* 2006), which is as good as the milk protein and other high-quality animal proteins. With sufficient processing and modification, the quality of soy protein could be improved above that of animal proteins (Sui *et al.,* 2021). Consequently, soy protein could replace the animal protein for vegetarians, and be a valuable and economical protein source for people allergic to milk proteins (Elmadfa and Meyer 2017).

Health benefits of soy proteins: Since most protein would be hydrolyzed to amino acids in digestive system, the most important value of soy protein for human beings is its nutritional value: providing abundant and well-balanced amino acids intake. For the body would not synthesize excess amino acids for storage, this nutritional value becomes extremely important. Though soybean crude protein lacks of methionine, tryptophan and cystine, it is still a high-quality protein for human beings. Soy protein is abundant in leucine, glutamic and aspartic acid (Van Etten *et al.,* 1959). Lack of amino acids intake in dairy diets could lead to a lot of health problems. For instance, lack of branched-chain amino acids (including leucine, valine and isocyanine) in human diets could result in metabolic diseases, and sulphur containing amino acids are related to age-related disease significantly (Rose 2019).

Soy protein could prevent cancers. Protein would also be hydrolyzed to bioactive peptides in digestive system, therefore, many peptides would affect human health, such as Bowman-Birk inhibitor (Birk 1985), an anticarcinogen from soybean. There are two possible assumptions to characterize the mechanism of BIB against tumor. One is that the inhibitor-protease complexes formed *in vivo* can act as free radical traps whereby the free electrons of hydroxyl or other radicals that can damage DNA are dissipated to sulfur atoms of the cystine-rich inhibitors or complexes (Ware *et al.,* 1999). Another possibility is that the carcinogens could be physically adsorbed by insoluble dietary fiber when it passes through the digestive tract. The insoluble inhibitor complex could play a role like insoluble dietary fiber, thus preventing cancer induction. In addition, a recent study reported a protease, one of bioactive peptides, could inactivate SARS-CoV-2 virus *in vitro* (Oba *et al.,* 2021), implying that it possesses potential ability to resist and prevent corona virus disease, probably COVID-19.

Soy protein could reduce the risk of cardiovascular diseases well. It has been recognized that increasing the intake of plant protein could result in not only significant low contents of low-density lipoprotein (LDL), cholesterol and plasma triglyceride, but also an increased level of high-density lipoproteins (HDL) in vivo (Messina *et al.,* 1994). The low ratio of LDL to HDL and low plasma triglyceride levels could reduce the risk of cardio vascular disease (Friedman and Brandon 2001). A possible mechanism characterized this process shows that soy protein exhibits its cholesterol-lowering effect through modulating the LDL receptors *in vivo*. Although this mechanism is still indistinct, several epidemiologic studies have found that the increasing soybean and soy foods in diets induce a significant decrease in plasma levels of LDL cholesterol of both normocholesterolemic and hypercholesterolemic men (Friedman and Brandon 2001), and consequently reduce the risk of cardiovascular disease.

Soy isoflavone and its health benefits: Soy isoflavone, a sub-group of flavonoids, is a class of polyphenolic compounds exclusively occurred in legumes. The word "phytoestrogen", which is usually used to refer isoflavones, comes from the Greek term for plant ("phyto-") and from the term "estrogen", that is a hormone that influences the female fertility in vertebrates (Křížová *et al.,* 2019). Isoflavone was noticed in 1940s for the first time (Bennetts *et al.,* 1946), because it is in connection with the clover disease, and therefore could influence the reproduction of ewe, as well as felid and rodent (Bennetts *et al.,* 1946; Chen *et al.,* 2021). The perspective that the isoflavones contain estrogen-like bioactivity has been widely accepted. Nowadays, isoflavone has been extensively applied in health products and bio-pharmaceuticals.

As shown in Fig.2, there are four main categories of isoflavones, including aglycones, glucosides, acetylglucosides and malonylglucosides (Heim *et al.,* 2002), and each category could be further classified into three kinds. The aglycones which could be divided into daidzein, glycitein and genistein. The components of glucosides are: daidzin, glycitin and genistin. The acetylglucosides include acetyldaidzin, acetylglycitin and acetylgenistin, while the malonylglucosides include malonyldaidzin, malonylglycitin and malonylgenistin.

The aglycones are directly derived from the phenylalanine pathway, and can be synthesized into glycosides by the glycosylation with UDP-Glucose, while glycosides can be further synthesized into other two main categories by the increase of acetyl or malonyl group (Fig.2). The isoflavones are conferred the solubility, stability and transportability by glycosylation and malonylation, and therefore suitable for storage in vacuoles (Yu *et al.,* 2008). Thus, although the major bioactive components of isoflavones are aglycones, the glucosides and malonyl-glucosides, the major storage form of isoflavones, are the most abundant components in the plant kingdom (Ku *et al.,* 2020). Consequently, approximately ninety percent of total isoflavones are glucosides in soybean seed. Meanwhile, malonyl-glucosides might be more stable compared with other categories, for it could be resistant to enzymatic degradation, thus increasing the retention of the molecules inside vacuoles (Sohn *et al.,* 2021).

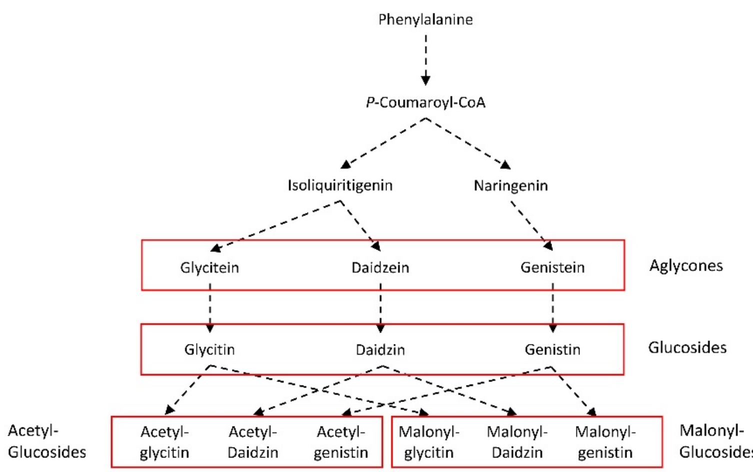

Fig.2 The biosynthesis of 12 kinds of isoflavone

Health benefits of isoflavone: The major sources of dietary isoflavones for humans are legumes and its products. Among more than 18000 kinds of legumes, soybean contains 10–100-fold higher levels of the major isoflavone (de Kleijn *et al.,* 2001). Therefore, soybean and soy-derived foods are the uppermost food sources of dietary isoflavones. According to a series of epidemiological studies, Asian diets generally have a 100-fold higher level of isoflavones compared with Western diets, because of a significantly higher ratio of soybean and soy-derived foods in Asian daily diets (Dixon 2004). In addition, these studies also showed that this difference in isoflavones intake is inversely correlated with breast cancer incidence in these two groups, indicating that isoflavone exhibits great potential value for the precaution and treatment of breast cancer.

Generally, isoflavone could affect estrogen signal transduction pathway and positively impacts human immunity in many ways, such as resisting breast cancer and reducing blood pressure. Although the molecular mechanism of how isoflavone could influence human immunity is not clear yet, recent reports suggested that this bioactivity is significantly related to its structure. Since soy isoflavone is similar to estrogenic structurally, it could compete with estrogen and testosterone (a kind of androgen) for binding with human sex hormone binding globulin (SHBG) (Zaheer and Humayoun Akhtar 2017). Consequently, isoflavones can potentially regulate the concentration of androgens and estrogens *in vivo* (Ganai and Farooqi 2015), and thus exhibit the availability of the sex hormones to target cells and organs. In addition, the structural features of isoflavones also confer ability to bind with estrogen receptor (ER) in human body, and therefore, exhibit both estrogenic and antiestrogenic activity (Dixon 2004).

Isoflavone could compress hormone-dependent cancers, such as urinary tract cancer and breast cancer. As many clinical and epidemiologic studies reported, the intake of isoflavones is significantly correlated to the inhibition of hormone-dependent cancers. Isoflavones could exhibit estrogen-like bioactivity to bind with ER, and ER is generally found in prostate secretory epithelium, brain, urinary tract and breast cells (Chen and Chen 2021). This may be an important factor for the strong correlation between isoflavones and hormone-dependent cancers compression. Moreover, there are two kinds of ER in human cells: ER-α and ER-β. ER-α activation is proved to stimulate cell proliferation in the breast tissue, while ER-β participates in proliferation inhibition and apoptosis stimulation (Křížová *et al.,* 2019). Isoflavones have higher ER-β binding activities, compared with ER-α, thus isoflavone could regulate the activity of ER-β through binding with this receptor and control the proliferation inhibition and apoptosis stimulation of hormone-dependent tumor cells (Dixon 2004).

Isoflavones could also relieve postmenopausal ailments for women, such as osteoporosis. The osteoporosis is a public health problem, which is usually endemic in postmenopausal women. The bone formation and resorption are regulated by estrogen signal transduction pathway in vivo, especially ER-β mediated pathway, thus isoflavones, bioactive compounds with extremely high ER-β binding activities (Maruyama *et al.,* 1998), could alleviate loss of bones theoretically. For the postmenopausal women are deficient in estrogen, their bone resorption would be increased while their bone formation would be decreased, resulting in their overall bone loss finally. However, isoflavones intake could make up the lack of estrogen. The osteoblastic bone formation could be activated by isoflavones, and the osteoclastic bone resorption could be repressed, and therefore, the overall bone loss would be prevented (Maruyama *et al.,* 1998). The mechanisms for these effects include stimulation of proliferation of osteoblast (bone forming) cells and protection of such cells from oxidative damage, and increased apoptosis of osteoclast (bone destroying) progenitor cells (Dixon 2004). In addition, isoflavones could relieve other postmenopausal ailments as well, including perspiration during sleep and vaginal dryness (Perez-Vizcaino and Fraga 2018).

Isoflavones could benefit to prevent cardiovascular diseases well. Cardiovascular disease is indeed a complex disease, whose pathogenesis involves various inducements, including estrogen deficiency (Chan *et al.,* 2008). The contents of LDL and cholesterol could be regulated by ER-β mediated estrogen signal transduction pathway. A low estrogen level could elevate the contents of LDL and cholesterol *in vivo*, then LDL would penetrate the blood vessel walls and be oxidized by free radicals, resulting LDL accumulate and plug the blood vessels and thereby causing thrombosis (Dixon 2004). Finally, the endothelial function would be destroyed. Therefore, isoflavone, an estrogen substitute, might be able to prevent and relieve cardiovascular events.

In addition, according to previous epidemiological investigations and clinical reports, isoflavones could also benefit to maintain thyroid functions, improve cognitive function, relieve metabolic syndrome, diminish inflammation, boost immunity, and affect reproduction (Křížová *et al.,* 2019; Chen *et al.,* 2021). Thus, soybean isoflavones might be the most important bioactive components for human health and immunity.

Other components and their benefits:

Soybean oil and its benefits: Soybean oil is one of the major components in soybean, which is a crucial cooking ingredient in many parts of the world, and impacts human health and immunity in many ways. For instance, it could reduce the plasma cholesterol and resist the thrombosis. Unlike animal oil, soybean oil is rich in unsaturated fatty acid (UFA), particularly linoleic acid, a kind of essential fatty acid (EFA)(Isanga and Zhang 2008). Meanwhile, linolenic acid, the other EFA in soybean is enough for human daily diet. UFA is extremely important for human beings, for it could maintain the relative fluidity of cell membranes to confirm cell physiological status, esterify cholesterol and lower triglyceride in the blood. UFA is also the precursor of prostaglandin, a bioactive factor in human body which could decrease blood viscosity and promote blood microcirculation (Zhou *et al.,* 2020). In addition, soy oil and its products also contain many important bioactive compounds including phospholipid, acetyl choline (ACH), which play a vital role in the growth and development of human beings (Clemente and Cahoon 2009; Zhang *et al.,* 2017).

Saponins and Its benefits: Saponins, bitter-tasting terpene glycosides, are amphiphilic molecules formed by compounds of a steroid or triterpenoid aglycone linked to one or more oligosaccharide moieties, which are found in many plants, particularly in soybean. Soybean is the primary source of saponins in human diets, as it contains 0.5–2% saponin. Saponin could resist HIV, prevent osteoporosis and lower cholesterol level, as well as contain antioxidative activity. The most important bioactivity of soy saponins for human immunity is its anticancer activity: growth inhibition of tumor (Isanga and Zhang 2008).

Research indicated that inflammatory cells could release reactive nitrogen, active oxygen and other pro-inflammatory factors, which could initiate and facilitate tumor by breaking DNA sequence. Meanwhile, pro-inflammatory factors promote the further deterioration of cancer, including tumor cell migration and growth. However, saponin could indirectly inhibit tumor cell migration and growth through its anti-inflammatory action (Elekofehinti *et al.,* 2021). Thus, the anti-inflammatory activity of saponin could be used to develop preventive medicine for anti-inflammatory and anticancer.

Phytosterol and its benefits: Phytosterol, a kind of isoprenoid compounds, is widely found in oil seed, which is structurally similar to cholesterol (Isanga and Zhang 2008).There are three kinds of phytosterolin soybean: β-sitosterol, campesterol and stigmasterol. These components are being developed as functional food ingredients and famous for their wide variety of benefits for human immunity (Choi *et al.,* 2007). For instance, it could decrease blood cholesterol levels and reduce the intestinal absorption of dietary and endogenous cholesterol, *via* binding with bile acids and prevent their re-absorption. Moreover, the antiangiogenic activity of phytosterol is a hot research field all the time, studies supported that phytosterol could inhibit the angiogenic action *via* a suppression of endothelial cell proliferation and capillary differentiation (Choi *et al.,* 2007). In addition, phytosterol could also exhibit prostatic hyperplasia suppression activity and the activity of plasminogen-activating factors.

Benefits of soybean derived products for human immunity:

Soybean is abundant in nutritional and immune ingredients for human. Recent studies have found that soybean and its derived products have great potential for human immunity, as well.

Soya-based infant formulas have attracted many consumers to replace the milk-based infant formulas (Vandenplas *et al.,* 2014). The soya-based infant formulas could not only be abundant in soy protein, but also provide well-balanced essential fatty acid, isoflavones and several beneficially bioactive compounds, which could not be obtained from other infant formulas (Chen and Rogan 2004). This indicates that soya-based infant formulas could be a major source of milk powder for children and adult's daily intake. Meanwhile, soy milk could provide high-quality protein for the people from underdeveloped country and area by virtue of the advantage of low-cost and easy to process (Friedman and Brandon 2001).

Soybean might resist COVID-19, one of the greatest enemies of human beings currently. For example, El-Hawary *et al.,* (2021) used docking analysis to investigate the soybean-associated endophytic fungi, and reported that it could be potential source for anti-COVID-19 metabolites. Meanwhile, recent reports presented that the extract of a Japanese fermented soy-derived food, natto, can directly inhibit viral infections including SARS-CoV-2 in vitro (Oba *et al.,* 2021). In addition, the bioactive substances in soybean seed, such as riboflavin, pyridoxine and nicotiana might have been found in having potential effects on COVID-19 (Keflie and Biesalski 2021). Thus, it is prospected that soybean and soy-based products could be an effective food for enhancing human immunity in the future.

Conclusions

Soybean has been one of the most important economical crops in the world, whose annual yield is more than 3.34 hundred million ton in the world. Soybean and soy-derived foods has been also permeating daily diet and cuisine culture of the world, for it is a healthy, safe, delicious and natural food for human being around the world.

Major compositions of soybean seed include soy protein, soy isoflavone, soybean oil, saponins and phytosterol, which have a great impact for human health and immunity. Soy protein could provide all the essential amino acids and a good balance in amino acid composition, and is strongly correlated with lower cholesterol levels. Soy isoflavone could reduce blood pressure, lower blood cholesterol, improve the cognitive ability of human brain and relieve menopause syndrome. Soybean oil exhibits the bioactivity of reducing the plasma cholesterol, while saponins has the functions of resisting HIV and preventing osteoporosis. As for phytosterol, it could decrease blood cholesterol levels, as well as reduce the intestinal absorption of dietary and endogenous cholesterol. Soybean and its derived products have great potential in enhancing human immunity. In brief, soybean, a tiny seed comes from China, is of both highly nutritional and medical value, and therefore, feed and protect billions of people in the world.

Acknowledgement

This chapter was financially supported by Strategic Priority Research Program of Chinese Academy of Sciences (XDA24030403 and XDA28070402).

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