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Anti-nutritional characteristics and mechanism of soybean agglutinin

Li PAN[1]; Jiawei LIU[1]; Mohammed Hamdy FAROUK[2,*]; Guixin QIN[1,*]; Nan BAO [1]; Yuan ZHAO[1]; Hui SUN[1]

[1] Key Laboratory of Animal Production, Product Quality and Security, Ministry of Education, Key Laboratory of Animal Nutrition and Feed Science, College of Animal Science and Technology, Jilin Agricultural University, Changchun, 130118, China
[2] Animal Production Department, Faculty of Agriculture, Al-Azhar University, Cairo, 11884, Egypt

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Abstract: Soybean agglutinin (SBA) is an important anti-nutritional factor in soybean. SBA can induce animal growth inhibition, cause pathological changes of intestinal tissue, and decrease in the immune system functioning. Recently, a great deal of research has been done on the effects of SBA on cell morphology, division, apoptosis, autophagy, as well as the correlated signal transduction pathway. This review mainly covers the chemical and biological characteristics of SBA, describes the multifaceted aspects of SBA anti-nutritional functions, and highlights the possible cellular and molecular mechanism of anti-nutritional effects of SBA. This review has important implications for the prevention and treatment of SBA-induced diseases, drug development, processing techniques of plant products, prevention of food- borne toxins, as well as human and animal health protection.

Introduction

Soybean agglutinin (SBA), also known as lectin, is a major anti-nutritional factor (ANF) in soybean seeds and products. Such substance represents about 10% of the total protein in mature soybean seeds. SBA can resist the enzymatic digestion and keep its biological activity throughout the entire intestinal tract due to its stability of the structure (Carbanaro *et al.*, 1997; Draaijer *et al.*, 1989). SBA can interact with the mucosal cells of the digestive tract, and finally leading to a series of anti-nutritional effects on animals. At present, a large number of studies have been carried out to describe the chemical and biological characteristics of SBA and the anti-nutritional mechanisms of SBA.

Therefore, the herein review aims to describe the main chemical and biological functions of SBA, describes the multifaceted aspects of SBA anti-nutritional functions, and highlights the anti-nutritional mechanisms of SBA. This review provides some help for the systematic understanding of the related progress of SBA.

*Address correspondence to: Mohammed Hamdy Farouk, mhfarouk@jlau.edu.cn; Guixin Qin, qgx@jlau.edu.cn
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The main chemical and biological characteristics of SBA

The chemical characteristics of SBA

SBA has a typical four-stage structure of legume agglutinin with a molecular weight of 120 kDa, an isoelectric point of 5.81, a sedimentation coefficient of 6.05, and sedimentation with 7S protein in ultracentrifugation.

SBA is composed of four subunits, each of which has a molecular weight of about 30 kDa. Each subunit has a covalently linked oligosaccharide chain containing 9 mannose and 2 N-phthaloyl-glucosamine ($Man_9GlcNAc_2$).

The sugar chain of each subunit in SBA is covalently linked with the amino-N of the 75th aspartame residue of the peptide chain (Asn-75) in the form of an N-glp-glucosamine bond. The sugar chain is located at the atypical interface of the subunit and interacts with the amino acid residue of the adjacent subunit. Each subunit of SBA also contains a closely bound Ca^{2+} and Mn^{2+} (De Boeck *et al.*, 1984). Additionally, there have a lot of hydrogen bonds and hydrophobic forces between the two monomers in the SBA molecule. Therefore, SBA is more stable than other legume family lectins.

Based on the structure characteristic of SBA, it can form specific binding with N-acetyl-D-galactosamine or galactose (Vojdani *et al.*, 2020). Such specific-binding of SBA to the sugar is not targeted at the sugar molecules in plant cells but on the surface of microorganisms or animal cells. This specific binding of SBA is also the prerequisite and

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necessary condition for SBA to induce anti-nutritional effect (Dam and Brewer, 2010). Therefore, the residual SBA binds to the surface of intestinal epithelial cells and negatively affects the secretion and absorption of mucus in the digestive system (Kim *et al*., 2015).

Ubiquitous biological activities of SBA

Like other plant lectins, the basic biological function of SBA is to agglutinate animal red blood cells and promote cell division.

The understanding of SBA begun with its agglutination discovery. SBA possesses species-specific on erythrocyte agglutination activity (Liu, 2006). For instance, the most sensitive agglutination reactions are detected against rabbit and human red blood cells than the other species (Pereira *et al*., 1974). Liu confirmed that swine had less responsive than rabbits, and bovine erythrocytes can be only agglutinated at a specific concentration (Liu, 2006). In addition to the differences in animal species, the agglutination degree of SBA to erythrocytes is also affected by some physical or chemical factors. When SBA is polymerized due to chemical or physical factors, the monomers can cross-link with each other, and the sites of reactions with erythrocyte are also increasing, which enhance the agglutination activity of erythrocyte (Guesdon *et al*., 1979). Moreover, the degree of agglutination between red blood cells and SBA is greatly enhanced after trypsin or streptomycin treatment (Liu, 2006).

Another biological activity of SBA is promoting mitogenic activity. SBA can promote lymphocyte division, and enrichment of erythroblasts (Pusztai *et al*., 1991; Hivrale and Ingale, 2013). SBA can be bound to glycoprotein receptor on macrophage membrane in rat erythrocyte, and consequently enhances the differentiation and metabolism of macrophage. SBA binds to Caco-2 cells during the differentiation stage, rapidly enters into Caco-2 cells, changes the metabolic state of such cells, and finally stimulates the DNA for protein synthesis (Draaijer *et al*., 1989).

Effects of SBA on animal growth and health

As one of the main anti-nutritional factors in soybean, the content of SBA in mature soybean seeds is up to about 10% of the total protein. Although its biological activity can be removed by some appropriate methods (Huisman and Tolman, 1992), there will still be a certain amount of residues. Additionally, SBA can resist the degradation of protease *in vitro* and gastrointestinal tract (Carbonaro *et al*., 1997), which will be combined with gastrointestinal epithelial cells, be engulfed into the blood circulation system, and induce a wide range of systemic anti-nutritional responses. These responses are exhibited in different mammalian organs and the immune system (Greer and Pusztai, 1985; Pusztai *et al*., 1993). This leads to the decrease feed utilization, low growth, pathological changes, and even death.

In general, the effects of SBA on animal growth and health are mainly manifested in the inhibition of animal growth and development, the destruction of animal intestine structure and function, and the decrease of immune function.

Effects of SBA on animal growth and development

SBA causes growth inhibition and negatively effects on animal health. The effects of SBA on the growth performance of animals vary with the animals' age, species, and SBA dose (van der Poel *et al*., 1992). The addition of high-dose SBA in pig diet can increase the total nitrogen output of ileum and increase the loss of nitrogen in piglets, resulting in weight loss and diarrhea (Makinde *et al*., 1996; Matthew *et al*., 2015). When the SBA content in the diet was 0–1.2 mg/g, there was no adverse effect on the growth performance of rats fed for 20 days, but when the SBA concentration increased to 2.0 mg/g, the growth performance of rats decreased by 23% (Li *et al*., 2003).

The effect of SBA on monogastric animals was significantly greater than that on ruminants. This may be due to the fermentation of rumen microorganisms in ruminants, which reduces the biological activity of SBA. The effect of SBA on pigs was significantly greater than that on chickens. SBA in the diet can cause intestinal damage in piglets (Makinde *et al*., 1996; Schulze *et al*., 1995; Zhao *et al*., 2011; Pan *et al*., 2013). Although SBA used as a phospholipid source in larval fish diets, it decreases growth and survival rate in marine species (like Salmo gairdneri, fingerling channel catfish and rainbow trout (*Oncorhynchus mykiss*), and affect gene expression (Wilson and Poe, 1985; Buttle *et al*., 2001; Steven *et al*., 2010). Muscle histology observations showed hindered growth in SBA-fed larvae (Alves Martins *et al*., 2010).

SBA-induced structural and functional destruction of animal intestine

SBA with intestinal structure

SBA can damage the brush border, reduce the surface area of intestinal absorption, and affect the digestion and absorption of nutrients (Bardocz *et al*., 1995). The height of jejunal villi was significantly shortened, and the morphology of jejunum mucosa was changed after feeding with SBA (Grant *et al*., 1989; Meilinah and Jeanny, 2012). A high dose of SBA can also cause atrophy of intestinal microvilli, reduce cell viability, cause brush border membrane disorder, and increases the weight of the small intestine (Pusztai and Bardocz, 1996; Zang *et al*., 2006; Meilinah and Jeanny, 2012; Babot *et al*., 2016). SBA induces the atrophy of the microvilli, reduces the viability of the epithelial cells. Intestinal permeability and the morphology of the brush border are also impaired after the combination of SBA to the intestinal tract (Liener, 1986; Safa *et al*., 2013).

After the damage of the intestinal structure caused by SBA, the nutrient digestive and absorptive capabilities are also damaged. SBA can significantly impact the transportation of macro-nutrients (most notably glucose and amino acids) through the intestinal membrane (Huisman and Jansman, 1991; Casaubon-Huguenin *et al*., 2004; Babot *et al*., 2016).

SBA with digestive enzyme

SBA can reduce the number of intestinal brush border epithelial cells, inhibit the activity of various enzymes (Salgado *et al*., 2002), by mucosal cells through specific binding with the surface receptors of intestinal wall epithelial cells.

A little amount of SBA in a normal diet may decrease the trypsin activity and increase the amylase activity of amylase in the pancreatic juice (Pereira *et al*., 1974). SBA can inhibit the

activities of duodenal brush border enterokinase (Rouanet *et al.*, 1983), brush border maltase and sucrase of duodenum, jejunum and ileum, and the enterokinase and alkaline phosphatase secreted by intestinal mucosa (Fasina *et al.*, 2006). Li *et al.* (2003) confirmed that the addition of SBA to the diet decreases the activity of brush border enzyme in the duodenum, jejunum, and ileum of turkey. SBA affects the proliferation of intestinal epithelial cells, the amount of mucin secretion, and the composition of mucin by binding with the membrane cells of porcine large intestine epithelial cells, thus affecting the digestion and absorption of nutrients (Pan *et al.*, 2013).

Effects of SBA on immune system

Lagarda-Diaz *et al.* (2017) suggested that all lectins can interact with the immune system in varying degrees. SBA promotes the immune defense of the host by stimulating immune responses, influencing protein kinases, and manifesting chemopreventive properties.

SBA can induce a local inflammatory reaction. SBA increases the population of mononuclear cells, the numbers of $CD4^+/CD8^-$ lymphocytes, the expression of CD11/CD18 surface molecules, and the number of circulating neutrophils and by inhibiting neutrophil migration in rats. An inhibitory effect on neutrophil migration is also observed in the absence of SBA present in the blood circulation (Benjamin *et al.*, 1997). The continuous feeding of SBA leads to a decreased immunological response in rats by inhibiting the intestinal mucosal immune system (Rohe *et al.*, 2017).

Cellular and molecular mechanism of anti-nutritional effects of SBA

Toxic effects of SBA on the cellular biological process in intestinal epithelial cell

SBA has a specific binding with the gastrointestinal tract. This specific binding is a precondition for deleterious toxic or side effects (Babot *et al.*, 2016). SBA can affect a variety of biological processes in the gastrointestinal epithelial cells, such as cell permeability, cell proliferation, apoptosis, autophagy, and signal transduction, etc. (Ramdath *et al.*, 2017; Lagarda-Diaz *et al.*, 2017; Xiao *et al.*, 2018).

SBA has been investigated in poultry diets, and it has the ability to bind to the intestinal epithelium and to induce cytotoxic damage on intestinal epithelial cells of broiler chicks (Babot *et al.*, 2016).

Pan *et al.* (2013, 2018a) have shown that SBA damages the integrity of the cell membrane, increases the permeability of the cell membrane, lowers the relative protein expression of occludin and claudin-3, damages the cell morphology, as well as lower the proliferation rate of the cells through the perturbation of cell cycle progression in IPEC-J2.

In other cell lines, SBA induces DNA laddering in a dose-dependent manner and causes DNA fragmentation in HeLa cell lines (Dey, 2013). SBA mediates autophagy, apoptosis, DNA damage in a dose-dependent manner in HeLa cells (Panda *et al.*, 2014). SBA induces autophagy and apoptosis of tumor cells in Dalton's lymphoma-bearing mice (Panda *et al.*, 2014).

The possible pathway of SBA-induced cell apoptosis and autophagy

In addition to the direct effects on the structure and biological function of intestinal epithelial cells, SBA can also affect the expression and function of cellular membrane proteins of the gastro-epithelial cells. These effects can be extended to cause cell apoptosis, autophagy and signal transduction.

SBA can use a mechanism to alter cell activity through the mitochondria-mediated pathway. SBA induces apoptosis and autophagic death through ROS generation in HeLa cells (Mukhopadhyay *et al.*, 2014b; Panda *et al.*, 2014). SBA induces cell apoptosis and decreases the mRNA expression of Bcl-2 in IPEC-J2F (Pan *et al.*, 2018b).

In addition, SBA induces some structural proteins to alter the cellular biological function. The integrins are involved in SBA-induced IPEC-J2 cellular viability. SBA can indirectly change the expression and function of integrins by binding with α-actinin-2, and then affect the proliferation, cycle and apoptosis in IPEC-J2 cells (Pan *et al.*, 2017, 2018b). In addition to integrin, there may be other proteins involved in the pathway of SBA-induced cell biological function change. As described before, the specific binding of SBA to intestinal epithelial cells is the premise for its anti-nutritional effect. Pan *et al.* (2018b) have identified a variety of SBA-specific binding proteins on IPEC-J2 cell membrane. According to the functional differences of these binding proteins, they can be divided into cytoskeletal proteins (such as keratin, actin, annexin, ankyrin, etc.) and kinases. Some of the cytoskeletal proteins are not only the framework of cells but also the role of messenger transmission. Additionally, some cytoskeletal proteins also play an important role in maintaining the morphology and function of cells. Therefore, these cytoskeletal proteins may be also involved in cell biological function alterations caused by SBA. However, further studies are needed to confirm such problems.

There is limited data available about the similarities among the structure of lectins. However, Liener (1986) has found that lectins are common toxic in most legumes. Grant and van Driessche (1993) also presented that there are some common structural and functional characteristics among SBA, other legumes or, plant lectin. Nowadays, the mechanisms of apoptosis and autophagy induced by SBA still need further research. Therefore, we can refer to the mechanism of other legume or a specific plant agglutinin to the causes of induced apoptosis and autophagy. Therefore, we can gradually improve the relevant mechanism, which leads to a change in biological functions caused by SBA.

Mechanism of apoptosis and autophagy induced by other legume lectins

Other legume lectins can also cause cell apoptosis and autophagy. Haemagglutinin (PHA-E) of dark red kidney bean can inhibit the proliferation of leukemia L1210 cells. Pea lectin induces apoptosis and cell cycle arrest in colorectal cancer SW480 and SW48 cells (Islam *et al.*, 2018). The production of apoptotic bodies can be induced by autumn purple bean lectin, and the apoptosis of breast cancer MCF-7 cells is induced by French bean haemagglutinin. Also, small glossy black soybean lectin can

obstruct the spread of breast cancer MCF-7 cells and hepatoma HepG2 cells (Lin *et al*., 2008).

The pathways of other legume lectins-induced apoptosis, autophagy, or both biological processes, are mainly occurred through the mitochondria-mediated pathway, death receptor pathway, and sugar-binding specificity pathway. Concanavalin A (Con A, a lectin, originated from the jack-bean) induces apoptosis in human melanoma A375 cells through the caspase-dependent pathway and induces autophagy in hepatoma cells through internalization and mitochondrion-mediated pathway (Lei and Chang, 2007). Con A induces cell apoptosis by down-regulating different signaling pathways mediated through NF-kβ, ERK, JNK, and Akt survival signaling (Amin *et al*., 2007; Helal Uddin Biswas *et al*., 2006; Sina *et al*., 2010). Con A can induce autophagic cell death in hepatoma cells through a mitochondria-mediated pathway (Fu *et al*., 2011). Peanut agglutinin induces apoptosis and autophagic death through ROS generation in HeLa cells (Mukhopadhyay *et al*., 2014a; Panda *et al*., 2014). *Sophora flavescens* lectin (SFL) has been reported to induce tumor cell death through a caspase-dependent apoptotic pathway, and its apoptotic mechanisms are speculated to be the death-receptor pathway (Liu *et al*., 2008). Lectins from *Phaseolus coccineus* L. induce the caspase-dependent apoptosis in L929 cells by a sugar-binding specificity (Chen *et al*., 2009).

Mechanism of apoptosis and autophagy induced by other plant lectin

Plant lectin, a class of highly diverse non-immune origin and carbohydrate-binding proteins, can induce apoptosis, autophagy, or both biological processes. Lectins from *Tragalus membranaceus*, *Astragalus mongholicus*, *Bauhinia forticata*, *Griffonia simplicifolia*, and *Lotus corniculatus* have the ability to inhibit cell proliferative activity and to induce cell apoptosis (Huang *et al*., 2012; Rafiq *et al*., 2013; Silva *et al*., 2014; Yan *et al*., 2009). Del Monte banana lectin delays the proliferation of L1210 cells (a mouse lymphocytic leukemia cell line) and HepG2 cells (a human liver cancer cell line) (Allen *et al*., 2009). Moreover, Ricinus agglutinin (RA) showed both anti-proliferative activity and autophagic cell death in Glioblastoma (the most malignant intrinsic glial brain tumor) cells (Sahoo, 2015). *Sclerotium rolfsii* lectin strongly inhibits cell proliferation and induces apoptosis of MCF-7 and ZR-75 human breast cancer cells (Savanur *et al*., 2014). *Solanum tuberosum* lectin inhibits Ehrlich ascites carcinoma cell growth by inducing apoptosis and G2/M cell cycle arrest (Kabir *et al*., 2016).

Based on an enormous amount of research, the plant lectins eliminate various types of cancer cells via different major pathways, that including direct ribosome inactivating, endocytosis-dependent mitochondrial dysfunction, sugar-containing receptors binding (Shi *et al*., 2017), also the death-receptor mediated pathway (Shi *et al*., 2013). In detail, the possible mechanisms related to the induction of apoptosis and autophagy by plant lectins may be due to the effects of lectin on the protein expression of Bcl-2, autophagy molecules, caspases, p53, ERK, Ras-Raf, BNIP3, and ATG families (Jiang *et al*., 2015; Yau *et al*., 2015). *Sephora flavescens* lectin with mannose specificity causes apoptosis through a death receptor-mediated caspase-dependent pathway in HeLa cells. *Polygonatum odoratum* lectin (POL) induces cell apoptosis and autophagy in human MCF-7 breast cancer cells by the Ras-Raf-MEK-ERK signaling pathway (Ouyang *et al*., 2014). *Korean mistletoe* lectin (*Viscum album* L. var. *coloratum* agglutinin) causes apoptosis in human hepatocarcinoma cells via the mitochondrial controlled pathway, which is independent of the p53 pathway and the p21 pathways (Lyu *et al*., 2002).

These related studies indicated that legume lectin and plant lectin have similar pathways in inducing apoptosis and autophagy. Such pathways are involving mitochondria-mediated, death receptor, sugar-binding specificity, and direct ribosome inactivating pathway, and other critical impacts such as apoptosis, and autophagy of intestinal cells.

Apoptosis, autophagy and their relationship

In addition to the pathway described above, to further reveal the signal transduction pathway of apoptosis and autophagy induced by SBA, we need to thoroughly analyze the pathway of cell apoptosis, autophagy, and the relationships between them. Apoptosis and autophagy are important indicators of animal health, since they are programmed cell death processes. Consequently, many studies have been conducted on the signal pathway for apoptosis and autophagy, as well as their mutual interactions.

Apoptosis and its pathway

Apoptosis, is defined as cellular Type-I programmed cell death. It is a conservative and orderly process of cell death. Such an active cell death process involves gene activation, expression and regulation. The character of apoptosis is the condensation of the cytoplasm and nucleus, DNA fragmentation, migration of chromatin to the nuclear periphery, cell contraction, dynamic membrane blebbing, and phagocytosis (Hengartner, 2000).

Apoptosis removes aging and abnormal cells in time, and plays a scavenger role. Apoptosis is triggered by three ways, including extrinsic apoptotic pathway, intrinsic apoptosis pathway, and endoplasmic reticulum pathway. The first one is surface death receptors (DR), as called extrinsic apoptosis. In the extrinsic apoptotic pathway, after the binding of cell surface receptors to specific ligands, apoptotic signals are subsequently activated and transmitted, finally enabling the cleavage of caspase-3, 6, and 7. The second way is the mitochondrial release of cytochrome c, called intrinsic apoptosis. In the intrinsic apoptosis pathway, mitochondrial outer membrane permeabilization (MOMP) is induced by the dimerization of pro-apoptotic proteins (Bax and Bak), then cytochrome c is released into the cytosol from the mitochondrial membrane. Subsequently, apoptosome is initiated by the binding of cytochrome c to apoptotic protein activating factor-1, the activates caspase-9, followed by the activation of caspase-3 (Gamie *et al*., 2017; Richa and Kristin, 2015; Safa, 2019). The third pathway is the endoplasmic reticulum pathway. Endoplasmic reticulum stress (protein misfolding or unfolding, endoplasmic reticulum stress) can lead to intracellular calcium overload or calcium homeostasis imbalance. On the one hand, caspase-12 was activated, and caspase-12 further activated

caspase-9 to promote apoptosis. Yet, Bax and Bak, the pro-apoptotic proteins in the Bcl-2 family, are activated to induce apoptosis (Ghavami *et al*., 2009; Wang *et al*., 2019).

Autophagy and its pathway

Autophagy, known as Type-II programmed cell death, refers to an evolutionarily conserved, multi-step lysosomal degradation process in which a cell degrades long-lived proteins and damaged organelles (Saha *et al*., 2018). The autophagy process includes the recycling of materials and energy, degrading damaged organelles or removing macromolecular substances in cells, participating in the renewal of endoplasmic reticulum, peroxides and mitochondria. Autophagy is involved in cell differentiation, cell development, and cell remodeling at the subcellular level, etc. Therefore, autophagy is essential for cell growth, differentiation, and metabolism, and for the maintenance of homeostasis (Levine, 2005).

Autophagy can regulate cell death with dual natures (mild or severe). Mild autophagy can protect cells from harmful conditions to some extent and promote cell survival, while severe or rapid autophagy can induce programmed cell death. Nowadays, the autophagy pathway includes the autophagy-dependent on the membrane target of rapamycin (mTOR) pathway, and the autophagy-independent of the mTOR pathway.

There are PI3K-Akt-mTOR signaling pathway, MAPK signaling pathway and other signaling pathways in the upstream of dependent mTOR signaling molecules, that regulate mTOR molecules and form complex network signaling pathways. Zhang *et al*. (2014) found that exogenous expression of apelin gene can inhibit the proliferation of pulmonary artery smooth muscle cells (PASMC) by the activation of the PI3K-Akt-mTOR signal molecule. When the intracellular energy decreases, LKB1 can phosphorylate and activate AMP-activated protein kinase (AMPK), which finally inhibits the activity of mTORC1 and then induces autophagy (van Veelen *et al*., 2011). Activated P38 MAPK (p38 mitogen-activated protein kinase) can also regulate the autophagy pathway in two ways after activation (Bak *et al*., 2016). Ammonia represents the independent mTOR autophagy, such as which can activate autophagy and prevent TNF-α induced apoptosis. In the liver, glucagon can also induce autophagy (Rabinowitz and White, 2010). In addition, there are also autophagy pathways that have been proved to be independent of the mTOR pathway, such as Beclin1, PI3K and Gai3 protein pathways.

The relationships between cell apoptosis and autophagy

There are positive or negative interconnections between apoptosis and autophagy (Huang and Klionsky, 2007), and this relationship between them may vary depending on their biological context (Cheng *et al*., 2008). Many classical apoptotic signaling pathways or proteins possess complex interactions with autophagy regulation (Gump and Thorburn, 2011; Su *et al*., 2013; He *et al*., 2018).

Both apoptosis and autophagy are regulated by some common factors and have some same biological functions. Interestingly, the activity of the apoptosis may be regulated by the autophagic pathway. The main relationships between apoptosis and autophagy may have different possible points.

First, apoptosis and autophagy promote each other. The expression of apoptosis gene and autophagy gene was up-regulated at the same time, and there were many regulatory molecules between apoptosis and autophagy (Wu *et al*., 2018). Bcl-2 family proteins play a key dual regulatory role between apoptosis and autophagy (Mariño *et al*., 2014). Second, autophagy is a necessary condition for apoptosis. For instance, inhibition of autophagy can delay apoptosis (Yang *et al*., 2011). Third, apoptosis and autophagy are antagonistic to each other as the induction of autophagy in melanoma can protect cells from chemical-induced apoptosis (Liao *et al*., 2011). *Rabdosia rubescens* (a Chinese herb) can play a toxic role through apoptosis and protect cells from apoptosis by autophagy pathway (Hassan *et al*., 2015). Zeng *et al*. (2012) investigated the interference of Atg5, 10, 12 and Beclinl which can significantly enhance the apoptosis induced by starvation. Such interference proves that autophagy may participate in the inhibition of apoptosis in the absence of nutrition. Fourth, autophagy and apoptosis are inhibited at the beginning and then are activated. At the early stage of some drugs, autophagy can protect cells from apoptosis. With the extension of time, the effect of apoptosis and autophagy can increase at the same time, and activate cell death (Kanzawa *et al*., 2003). Fifth, apoptosis and autophagy are the premise of each other. Inhibition of either side will lead to inhibition of the other side's action process. Therefore, autophagy and apoptosis at least interact in five biological points.

Prospects

Based on the structure and toxic effects of SBA on the cells (apoptosis and autophagy), it can be used in differentiating markers to study cancers and metastatic cell lines, helping in detecting the carbohydrate residues present on the cell surface (Dey, 2013; Lagarda-Diaz *et al*., 2017). Therefore, some positive effects of SBA are considered anti-cancerous. Hernández-Ledesma and Hsieh (2017) have demonstrated that SBA can inhibit the proliferation of human cancer cell lines such as BT20, HBL100, MCF-7, T47D, HepG2, and melanoma A375 cells. Because of its chemopreventive activity, SBA can be used to induce apoptosis and autophagy in future studies (Yau *et al*., 2015).

The specific binding of SBA with small intestinal epithelial cells is the prerequisite for its anti-nutrition effect, which will lead to apoptosis and autophagy. We can use these SBA characters to identify the SBA-specific binding proteins on the intestinal epithelial cell membrane. We can constantly uncover the signal transduction vector and possible signal pathway of SBA induced apoptosis and autophagy through *in vitro* nutrition environment and related gene expression cell control test, in order to achieve the purpose of preventing SBA from tissue damage.

In addition, the development of new technologies related to blocking or reducing the SBA anti-nutritional toxicity needs further investigation.

Summary

SBA is a major anti-nutritional factor in soybean, which may induce abnormalities in the biological and metabolic patterns of intestinal cells. It can be inferred that SBA acts in different

anti-nutritional mechanisms that including damaging the structure of the intestinal epithelial cells, blocking the cell cycle, promoting apoptosis, autophagy, altering the metabolic and related signal transduction pathways.

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