Biocatalysis and Agricultural Biotechnology 17 (2019) 710–719

Contents lists available at ScienceDirect

Biocatalysis and Agricultural Biotechnology

journal homepage: www.elsevier.com/locate/bab

Nutraceuticals derived from seed storage proteins: Implications for health wellness

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ARTICLE INFO

Keywords:
Bioactive peptides
Antimicrobial peptides
Angiotensin converting enzyme-II
Anti-viral
Anti-fungal
Anti-tumor activity

ABSTRACT

Seed storage proteins are major source of proteins because of readily available bioactive peptides. These peptides are fragments of a protein, which showed positive implications on human wellness and gained wide importance owing to their health benefits such as antimicrobial, antiviral, antifungal, anti-tumor activities. In plants, the bioactive peptides are ubiquitous in distribution that act as a part of innate response upon elicitation. In addition, these plant based bioactive peptides have structural similarity with the insect and animal sources. In most of the cases, the bioactive peptides triggers their response by binding the target membrane that results into permeabilization and rupture of the membrane. Delineating the potential of peptides having antiviral, antimicrobial and antiviral properties these can be used in the food and pharmaceutical industries. Further, these peptides can be used into the packaging material called active packaging that enhances the shelf life and quality of the food. In this review, seed storage proteins based bioactive peptides and their potent applications for health as well as food industry have been elucidated.

1. Introduction

Seed, in the course of plant evolution, is a unique attribute in gymnosperms and angiosperms responsible to endure during unfavorable conditions. Seed is a repository, which accumulates proteins, carbohydrates and lipids to facilitate nutrition and protection to the developing embryo and other tissues. Among these primary metabolites, proteins are playing a vital role in maintaining the normal plant cell metabolism. The proteins are classified mainly into two groups such as structural and biologically active proteins, whose functions are indispensable in structural architecture of cell (cell wall) and protection of cellular machinery like enzyme inhibitors, enzymes, lectins etc (Agarwal and Kumar et al., 2016). Recent studies emphatically advocating the great advantages of bioactive peptides, whose physiological functions have been manifested in the form of anti-viral and anti-tumor activities, immune-modulatory and reduces the cholesterol and blood pressure (Kumar et al., 2017). Considering the physiological actions of bioactive peptides and their potential for commercial viability, particularly anti-microbial and anti-viral activities helps to develop a novel and cost effective drugs that alleviate the resistance tendency of micro-organisms. (Kumar et al., 2016). Moreover, these health benefits of seed storage proteins (SSP) can be explored in active packaging, where the peptides are incorporated into the polymer to increase the quality and shelf-life of a product (Chandusingh et al., 2017b). Hence, in the paper, potential of bioactive peptides and their health benefits have been discussed with a focus on industrial applications that ultimately benefit the human wellness.

2. Seed storage proteins

Seed storage proteins (SSP) play a pivotal role in the human diet. It supplies the protein requirement to more than half of the global population, particularly for human and livestock (Chandusingh et al., 2017a). These proteins are abundant in nature and determines the quality of protein, as a result, these SSP's are widely preferred than the animal based proteins (Kumar et al., 2016). For instance, essential amino acids such as methionine and cysteine (sulphur containing amino acids) are inadequately available in legumes; in contrary, cereals

Abbreviations: Glucosaminoglycans, (GAG); Ribosome-inactivating proteins, (RIPs); Seed storage proteins, (SSP)

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https://doi.org/10.1016/j.bcab.2019.01.044
Received 11 October 2018; Received in revised form 16 January 2019; Accepted 17 January 2019
Available online 28 January 2019
1878-8181/

contain tryptophan, lysine and threonine that are significantly low. Hence, to supplement the adequate nutritious food, SSP having enriched essential amino acids can be nourished (Vinutha et al., 2014a). Seed storage proteins are synthesized either in endosperm or cotyledon and stores the protein moiety in the form of protein storage vacuoles (PSV) also known as protein bodies. At physiological conditions, these protein bodies are densely available in mature seeds, where the psv is embedded with the protein deposits (Singh et al., 2015).

Bioactive peptides are specific moieties of protein that influence the physiological functions and ultimately lead to health wellness (Chandusingh et al., 2017b). Bioactive peptides when released in the gastrointestinal (GI) region, play different functions such as anti-viral, anti-microbial, anti-tumor, anti-thrombic, anti-hypertensive, anti-oxidant and immunomodulatory that ultimately improves the health (Cizeau et al., 2000; Kumar et al., 2017). Assimilation of bioactive peptides in the GI region depends on the size, length and hydrophobicity of the peptide. For instance, mono and di peptides are actively transported via intestinal epithelium with the help of H^+ gradient, whereas, oligopeptides would transport through intestinal epithelium either by para cellular channels or pinocytosis based on hydrophobicity and size of the peptide (Sinha et al., 2016). However, after absorption, the peptides might be degraded by the action of serum protease released from the intestine. Hence, peptidase degradation resistant mechanism would be inevitable to exert the physiological role of SSP on the body, when administered through intra-venous or oral mode.

Seed storage proteins are classified into four types by Osborne and Campbell (1898), considering the criteria of solubility and extractability (Fig. 1). They are:

- Albumins [(1.6S–2S) (water soluble)]
- Globulins [(7S–13S) (soluble in dilute salt solutions)]
- Glutelins (soluble in dilute acid or alkali)
- Prolamins (soluble in water/alcohol mixtures)

Globulins and prolamins remain as oligomers and small aggregates, whereas, the glutelins form large disulphide bonded aggregates, whose solubility is poor in water (Singh et al., 2017). In dicots (eg. legumes), albumins and globulins occupies a major proportion; but in monocots (eg. cereals), glutelins and prolamines are pre-dominant in nature (Kumar et al., 2017). These SSPs, when undergoes GI digestion, releases the bioactive peptides from the protein by the action of hydrolytic enzymes.

3. Albumin (1.6-2S)

Albumins derived from plant proteins have similar characteristics as an egg albumin, which is able to coagulate. Later, these proteins were classified based on solubility in water and coagulable with heat. However, during extraction from tissues, salt availability at low concentrations in the tissues should be removed using dialysis techniques, otherwise obtaining true fraction of albumin is difficult. Albumins are generally found at lower concentration in seeds and the best characterized types are leucosin (wheat, barley), phaselin, legumelin and ricin from kidney bean, legumes and castor bean, respectively. Youle and Huang (1981) have extracted the seed storage proteins using sucrose gradient ultracentrifugation to compare salt soluble protein fraction from 12 different species covering legumes and grass (monocot). Ultracentrifugation separation showed three peaks such as 2S, II S and 7S, among which the 2S (cysteine) fraction is comparatively higher than the other fractions.

3.1. Structure of albumin

Seed storage albumins are abundantly available proteins that are soluble in water and are easily broken-down during seed germination to supplement nutrients such as sulphur and nitrogen for the seedling development. However, in seed maturation phase these proteins undergo post-translational modifications and trafficking before deposition with great stability and quantity in protein storage vacuoles. Ericson et al. (1986) has deciphered the primary structure of a processed and mature napin (an albumin). In this study, napin-type albumin precursor from rapeseed has been cloned, isolated and purified the matured napin. Structural studies on napin revealed that it is a heterodimeric 2S albumin protein, comprised of two subunits of 30–40 and 60–90 amino acid residues, respectively. 2S albumin synthesized as a precursor protein has been transported co-translationally into the endoplasmic reticulum lumen. In the post translational modifications, the protein undergoes conformational changes into a folded form by introduction of four intra-chain disulphide bonds with eight conserved cysteine residues, which further transported into the cell vacuole (O'Kane at al., 2004a). Moreover, in the vacuole, partial folded protein undergoes proteolytic processing that result into two subunits, which is stabilized by two disulphide bonds (Fig. 2a).

Apart from 2S albumins, various types of albumins exist that differ with the basic 2S albumins either in structural features or the route of synthesis in the cell (Monsalve and Rodriguez, 1990). For example, the

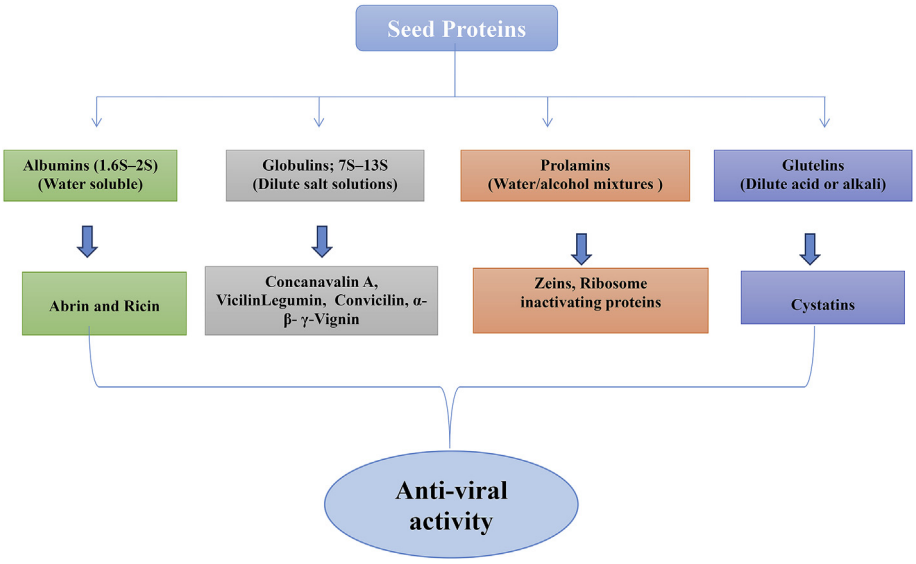

Fig. 1. Putative seed storage proteins responsible for anti-viral activity.

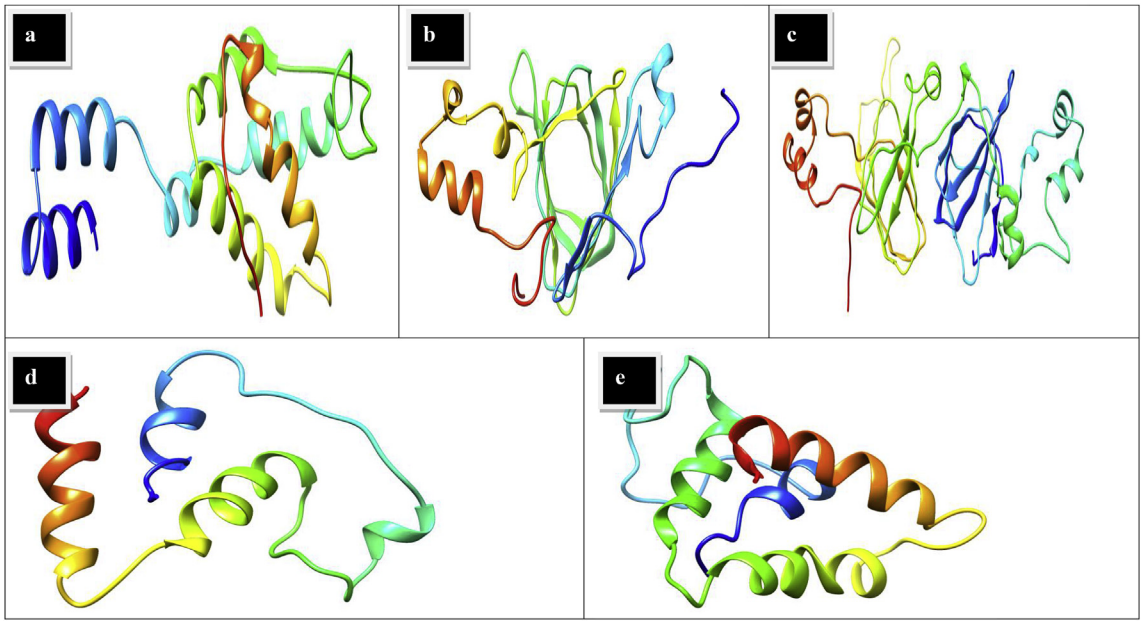

Fig. 2. Three dimensional structure of (a)2S albumin, (b) globulin, (c) convicilin, (d)glutelin and (e) prolamin (Modeller9v19 software).

Table 1
Albumins distribution in crops and their amino acid composition.
Source (Youle and Huang, 1981):

Family	Species	Protein			Amino acid	
		2S	7S	11S	Cys	Met
Cruciferae	*Brassica* spp.	60	0	38	9.01	2.60
Compsotae	*Helianthus annuus*	62	0	38	6.59	2.84
Linaceae	*Linumusita tissimum*	42	0	58	8.17	1.93
Leguminosae	*Lupinus polyphyllus*,	38	26	36	6.15	0.66
	Arachis hypogaea	20	6	74	1.81	1.84
Lecythidaceae	*Bertholletia excels*	30	9	61	13.11	17.33
Cucurbitaceae	*Cucumis sativus*	56	17	27	8.92	3.79
Betulaceae	*Corylus* sp.	28	12	60	10.27	3.69
Liliaceae	*Yucca* sp.	27	16	57	9.29	3.17
Malvaceae	*Gossypium hirsutum*	33	35	32	7.74	1.80
Euphorbiaceae	*Eicinus communis*	44	14	42	8.5	1.60

2S albumins of sunflower and castor bean are not cleaved subunits (Muren et al., 1996) because in these plants the 2S albumins are synthesized as a single pro-protein instead of two mature subunits (Mazhar et al., 1998; Sharief and Li, 1982). In addition to form of protein synthesis and its localization, variation has been noticed in the post translational modifications of albumins. Lupin is an albumin that shows an additional free cysteine residue and disulphide bond formation in conglutin; whereas, the pea albumin subunits PAla and PAlb is devoid of inter-chain disulphide bonds (Egorov et al., 1996). There is also considerable variation in the levels of cysteine and methionine contents in the 2S albumins as illustrated in Table 1.

4. Globulins (7S–13S)

The existence of globulin proteins is not only confined to animals but also found in plants predominantly as storage protein in seeds. These seed proteins binds with Human IgE antibodies and triggers allergic reactions (Sanchez-Monge et al., 2004). The seed storage proteins from graminae and leguminaceae species are sedimented at 7-8S and 11-12S, respectively (Danielsson, 1949). Hence, it is termed as 7S and 13S globulins that are popularly known as legumin and vicilin, respectively (Osborne and Campbell, 1898). The globulins in seeds contain higher molecular weight than albumins, as a result, these proteins

Table 2
Availability of globulin seed protein in different species and their relative molecular masses (Mr.).
Source (Casey et al., 1986):

Protein	Species	Mr x10^{-3}
Vicilin	*Pisum sativum*	150–190
	Vicia faba	150
	Vigna unguculata	170
Convicilin	*Pisum sativum*	220–290
	Phaseolum vulgaris	
Canavalin	*Canavalia* spp.	170
	Phaseolus vulgaris	140–163
β- conglycinin	*Glycine max*	150–210
Conglutin β	*Lupinus* spp.	185
12S		
Legumin	*Pisum sativum*	330–450
	Viciafaba	320–400
	Vigna unguiculata	300–400
Arachin	*Arachis hypogeae*	330–350
Comglutina	*Lupinus* spp.	315
Helianthinin	*Helianthus annus*	300–350
Cucurbitin	*Cucurbita* spp.	325
Glycinin	*Glycine max*	320–375
Cruciferin	*Brassica napus*	300

are soluble in salt solution instead of water. Abundance of globulin proteins in different species and their molecular mass are described in Table 2.

Globulin proteins can be separated using either anion exchange chromatography or native electrophoresis that could fractionate into three main components viz. α-vignin, β-vignin, and γ-vignin. Immunological studies depict that the α-vignin has structural homology between β-conglutin and β-vignin (the vicilin from *Lupinus* sp seeds); however, it differs in structural aspects between α- or γ-vignins and *Lupinus* sp. counterparts (Freitas et al., 2004).

4.1. Structure of globulin

The major seed storage globulin protein found in pea is known as legumin (11S), vicilin (7S) and convicilin (Barac et al., 2010; Sanchez-Monge et al., 2004). The legumin extracted from pea is a hexamer, whose molecular weight range between 320 and 380 kDa (Gueguen

et al., 1988; Heng et al., 2004). The six subunit pairs of mature legumin interacts non-covalently (Fig. 2b) and are divided into an acidic subunit (40 kDa) and a basic subunit of 20 kDa that are cross-linked by single disulfide bond (Shewry et al., 2006; Griga et al., 2007). The various legumin polypeptides of several genes have been identified, viz. 4–5 acidic (α) and 5–6 basic (β) polypeptides (Croy et al., 1980). The acidic polypeptides (38–40 kDa) are heavier in size than basic polypeptides (19–22 kDa).

Vicilin protein derived from pea is a trimer protein (170 kDa) where the cysteine amino acid residues are absent (O'Kane et al., 2004a; Gupta et al., 2018). Due to post-translational modifications (conformation folding), vicilin exhibited huge variation in the subunits composition (Fig. 2c). Structural features depicts that the vicilin protein consists of three subunits with molecular size of 47 kDa, 50 kDa, 34 kDa and 30 kDa, respectively (Schroeder, 1982; O'Kane et al., 2004b). A third major seed storage protein in pea is convicilin having the molecular size of 71 kDa (Cserhalmi et al., 1998). Convicilin is different in antigenic properties, when compared to legumin (Rangel et al., 2003). Convicilin differs from vicilin in structure, upon treated with antibodies the convicilin protein clearly separates from vicilin by non-dissociating techniques due to lack of vicilin subunits (Kimura et al., 2008; Martínez-Villaluenga et al., 2008; Guleria et al., 2009).

5. Glutelins

Glutelin proteins are highly resembling to prolamin like proteins in some of the grasses' that are soluble in chaotropic or reducing agents, dilute acids or bases and detergents. The wheat gluten proteins can be classified into two groups such as gliadins and glutenins and the former is soluble in alcohol while the latter remains insoluble in the alcohol (Table 3). Glutenins are huge polymers in nature (Shang et al., 2005; Dewar et al., 2006) and are rich in hydrophobic amino acids like phenylalanine, valine, proline, tyrosine and luecine (Elwart, 1967). Besides, it acts as the primary energy storage protein in the rice endosperm (Tiwari et al., 2017; Singh et al., 2015). Presence of glutenin in wheat is an important feature for refining baking properties and cross-link with other proteins by inter or intra disulphide bonds during baking (Fig. 2d). Glutelins are also reported in barley and rye in addition to wheat (Shang et al., 2005; Sinha et al., 2016). High molecular weight glutelin (glutenin) of the grass tribe *Triticaceae* can be used as sensitizing agents for coeliac disease in individuals possessing the HLA-DQ8 class II antigen receptor gene (Dewar et al., 2006).

6. Prolamins

Unlike other proteins and their solubility, prolamins (Fig. 2e) are one of the prominent seed storage proteins that serves as an important source for SSP. Based on the solubility criteria, prolamins that are able to soluble in aqueous ethanol (mercaptoethanol) are classified as first group prolamins and the second group of prolamins are insoluble in aqueous alcohol due to the presence of interchanged disulfide bonds. In addition to solubility, the cereal prolamins are also classified based on the molecular size and occurrence into following classess:

(i) Triticeae (wheat, barley, rye, and their relatives)
(ii) Oats
(iii) Rice and
(iv) Panicoideae (maize, sorghum, and prominent millets).

6.1. Prolamins distribution in triticeae

The prolamins derived from the triticeae family are rich in proline and glutamine amino acids. Further, the prolamins are divided into three families such as sulphur rich amino acids (S-rich) prolamines, high-molecular weight (HMW) prolamins and very low amount sulphur amino acids prolamins (S-poor). Sulphur rich prolamins are the predominant seed storage proteins, which can be recovered with an abundance of around 70–90% in a prolamins fraction (Okita and Rogers, 1996).

The low-molecular weight (LMW) glutenin, α-gliadins and γ-gliadins subunits of wheat, γ-secalin of rye and the β and γ-hordeins of barley all represent to group of prolamins. There are N-terminal repetitive and C-terminal non-repetitive domains present in the amino acid sequence of sulphur rich prolamins. The repeated short peptide motifs of amino acid are rich in proline and glutamine. Cysteine residues present in the non-repetitive domain forms bonding with disulphide rich prolamines (Cheng et al., 2010; Hernando et al., 2003).

The sulphur deficient (S-poor) prolamins consist of the ω-gliadins from wheat, ω-secalins from rye and C-hordeins from barley. The sulphur deficient prolamins have a repetitive and a non-repetitive domain near the N-terminus and C-terminus of proline and glutamine, respectively. The high molecular weight (HMW) prolamins that provide bread making quality contain three domains, which are rich in glycine and glutamine amino acids.

6.2. Prolamins distribution in oats and rice

The prolamins derived from the oats are called avenins, which share about 10% of the total seed proteins. Avenin seed proteins are similar in structure of triticeae prolamins due to the presence of repeated sequences. In case of rice prolamins, they are divided into four classes, namely- I, II, III, and IV, which share 5–9% of the total seed storage proteins and differs in structure of repetitive and non-repetitive sequences to triticeae prolamins. The classes of I-III are major and class IV is minor in distribution. The class IV is rich in sulphur containing amino acids, around 30% of methionine and cysteine amino acids can be retrieved from protein fraction (Yamazaki et al., 2008; Shibata et al., 2006). The amino acid sequence structure of class IV has low level of sequence homology with the other remaining three classes.

6.3. Prolamins distribution in panicoideae

Prolamins of maize seed storage protein are called zeins that divided into four major groups such as α, β, γ and δ zeins. These proteins can be separated from 27 kDa to 100 kDa using SDS-PAGE (Vinutha et al., 2014b). The α-zein protein is predominantly abundant (70%) in occurrence with the molecular size of 19–22 kDa followed by γ-zein (27-16 kDa). These proteins are rich sources of cysteine residues and are

Table 3
Glutelin proteins derived from the rice endosperm.
Source (Chen et al., 2010):

Classification	Protein names/Acc. No.	Iso-electric point (pl)	Molecular weight (MW)
Seed Storage proteins	Glutelin/31455453	6.60	35639
	Glutelin type I precursor/GLUA1_ORYSJ	9.9	56212
	Glutelin II precursor/A34332	8.93	56271
	Glutelin precursor/A27033	9.17	56274
	Glutelin/169791	9.17	55879
	Glutelin/31455453	6.60	35639

soluble in alcoholic solution containing a reducing agent and water. The β-zeins protein (10 kDa) and δ-zeins protein (18 kDa) are rich in methionine (Schuppan and Hahn, 2002; Reddy and Yang, 2011).

7. Seed storage proteins and their anti-microbial properties

7.1. Biological activity of abrin and ricin

Recent studies on 2S albumins particularly abrin and ricin have gained great interest because of anti-viral activity that reduced the formation of tumor (Domashevskiy and Goss, 2015; Gadadhar and Karande, 2013). Haemagglutination of trypsinized rabbit erythrocytes was demonstrated in the albumin fraction exclusively, which was strongly inhibited either by chitin or N-acetylglucosamine (Freitas et al., 2004; Wang et al., 2005). To evaluate the anti-cancer property and inhibitory effect of abrin and ricin, assays were conducted over human tumor growing as xenografts in nude mice. The growth of *in vitro* human tumor cell was inhibited over treatment with abrin (Fosted and Phil., 1997; Cavazos and Mejia, 2013). Further, several researchers reported that the abrin protein derived from *Abrus precatorius* seeds exhibited anti-tumor activity on sarcoma (Reddy and Sirsi, 1969; Lutsyk et al., 1977). Similar anti-tumor activity was also observed with ricin albumin (Mosinger, 1951; Lin et al., 1970b). Moreover, the peptides extracted from *Ricinus communis* and *Abrus precatorius* has been found to possess anti-tumor activity (Lin et al., 2003). However, the ricin compound should comparatively higher in concentration because the possibility of contamination with traces of intact toxin could impede the function of protein (ricin). Lin et al. (1970a) reported the effect of crystalline abrin and ricin on Ehrlich Ascites tumours in mice. They found that mice could be cured by treatment with abrin and ricin as late as 5 days after intraperitoneal injection, which could attained by killing the cells through inhibition of protein synthesis. Therefore, these studies corroborates the effectiveness of abrin and ricin seed proteins for the treatment of tumor inhibition.

7.2. Biological functions of globulin

Emerging evidence on anti-viral activity of globulins particularly vicilin like seed storage protein and concanavalin A shows that these proteins could be exploited for their biological function. In *Arabidopsis thaliana*, membrane or vesicle-packaged viral replication complexes (VRCs) are introduced over tobacco mosaic virus (TMV) infection during membrane transition of endoplasmic reticulum. Chen et al. (2013) have conducted microarray studies for screening of *Arabidopsis thaliana* genes responsible for inhibition of TMV infection in the initial infection stage. Interestingly, the *PAP85* (annotated as a vicilin-like seed storage protein) gene was up-regulated during 0.5–6 h of TMV infection. Further, it was noticed that the TMV accumulation was reduced in *pap85*-RNA interference (RNAi) *Arabidopsis*; whereas, it restored to wild-type when *PAP85* was over expressed in *pap85*-RNAi *Arabidopsis* (Chen et al., 2013). This study demonstrated that the TMV infection could be arrested using vicilin like seed storage protein.

Studies on putative anti-viral function supports with the observation on carbohydrate-binding concanavalin A (ConA) seed storage globulin protein that can agglutinate cancer cell (leukemic cells). Generally, leukemic cells were generated by simian virus 40, polyoma virus, X-irradiation and chemical carcinogens. Concanavalin A shall remain in non-agglutinated state in normal cells but can strongly agglutinates in transformed cell due to presence of α-methyl-D-glucopyranoside (α -MG) carbohydrate that have strong binding affinity to ConA. In contrary, carbohydrates like α -methyl-L-fucopyranoside or N-acetylglucosamine show either no affinity or very less affinity to ConA. In addition, bivalent metal ion is essential to agglutinate the concanavalin A protein.

In a study, it was revealed that withdrawing bivalent metal ion ($Mn2^+$) from α -MG binding site of the ConA protein lead to disappearance of the agglutination process (Miller and Krijnse, 2008; Salonen et al., 2005). Once the cell was treated with trypsin, the normal cells showed non-agglutination of normal cells but in the transformed cell, the agglutination reaction has been observed (Podolsky et al., 1974). Similarly, in another study, the normal 3T3 cells and rat cells were infected with simian virus 40 and polyoma virus, respectively. In both the cases, the infected cells have been observed with agglutination reaction within two weeks upon virus infection. Possible explanation for concanavalin-A anti-viral activity illustrates that the cancerous cell contain active sites on the membrane surface, which interact with α-MG sites and inhibit the multiplication of the virus. These studies corroborate that the globulin based SSP have huge potential to be used for health perspectives (Inbar and Sachs, 1969).

7.3. Biological functions of glutelin

Cystatins is one of the smallest proteins of glutelin family having 100 amino acid residues, which (approx.) showed anti-viral activity owing to proteinase inhibitors. Each protein have a central moiety of amino acids like Gln-Val-Val-Ala-Gly or related region, whose putative function is to interact with papain, a cysteine protease (Arai et al., 1995; Singh et al., 2013). Oryzacystatin was found in rice, which is known to be the first well-defined cystatin derived from plant origin. Recent molecular cloning and expression studies suggest that the similar cystatins were also found in corn and wheat. Cystatin and oryzacystatin derived from wheat and rice have been structurally demonstrated that they have an inhibitory effect on poliovirus and adzuki bean weevil because of cysteine proteinases in their digestive tract (Li et al., 2015). These promising results of cereal cystatins on defensive functions have prompted to produce transgenic rice with cystatin genes. Recent studies had introduced the cystatin genes and found stable expression of the introduced genes in the rice cultivar. The possible utility of these new rice cultivars with anti-viral compounds could usher new era of compounds responsible for health wellness.

7.4. Prolamines and their biological functional properties

Ribosome-inactivating proteins (RIPs) are derived from corn are naturally occurring potent toxins. Unlike other plant RIP's, maize synthesize RIP as an inactive precursor i.e. proRIP1 or b-32 that needs to cleave in order to bring into active form (Hank et al., 2004; Xiaomin et al., 2008). Hence, the proenzyme is subjected to proteolytic activation, whose action results in activation of proenzyme by removal of the N- and C-terminii and internal sequences. Similarly, another maize RIP such as RIP2 encoded by the *Rip3:2* gene has been characterized and found meager amounts in shoots, tassels, roots, silks and leaves. Unlike *Rip3:1* gene, the *Rip3:2* is not under the regime of *opaque-2* transcriptional activator (Au et al., 2016; Lappi et al., 1985; Bass et al., 2004). However, *Rip3:2* with up-regulation has been noticed in drought conditions that encodes a 31.1 kDa polypeptide having similar resemblance to proRIP1 inactive protein in regions corresponding to active protein and the NH_2-terminus extension. In both the proRIP2A and proRIP1 proteins, the former have 19-amino-acid internal moiety had very little similarity with the latter sequence despite of being rich in acidic residues (Narayanan et al., 2005; French et al., 1995). Bioassays on RIP activity showed that *Rip3:2* encode a polypeptide, which upon proteolytic cleavage possess RNA-specific *N*-glycosidase enzyme activity, an activated form as RIP 1 (Hank et al., 2004; Krishnan et al., 2002). Interestingly, these two RIP genes showed different regulations of seed proteins that indicate different roles probably either involved in defense-related functions or response to environmental stimulus (Legname et al., 1991; Laura et al., 2016). Some studies on role of RIP demonstrated that repressed fungal growth, insect feeding (maize RIP 1) and antiviral activity (Dowd et al., 1998; Krishnan et al., 2002; Yuan et al., 2002).

Table 4
Putative mechanisms for anti-viral activity of seed storage proteins.

Seed Protein	Plants Source	Molecular Size	Antiviral Activity	References
Pokeweed antiviral protein (PAP) and Ribosomes inactivating Protein (RIPs)	Phytolacca americana	Mr = 29000	Inactivate wide variety of eukaryotic ribosomes.	Bonness et al. (1994)
Ribosome-inactivating proteins (RIPs)	*Saponaria officinalis* *Agrostemma githago* *Asparagus officinalis*	Mr = 29000-32000	Inactivate wide variety of eukaryotic ribosomes.	Stirpe et al. (1983)
Cochinin B, a novel RIP	*Momordica charantia*	30 kDa	Inactivate influenza A	Pongthanapisith et al. (2013)
P1S and P2S (Sulphur derivative Protein)	*Azadirachtin indica*	80 kDa	Effective against poliovirus type 1	Galhardi et al. (2012); Godoi et al. (2014)
Ribosome-inactivating protein cucurmosin	*Cucurbitamoschata*	27 kDa	Anti-cancerous and induces apoptosis in tumor cell	Zhang et al. (2012)
Luffaculin 1	*Luffaacu tangula*	28 kDa	Inhibiting tumor cells	Hou et al. (2007) Barbieri et al. (2006)
Saporin L1 and Saporin SO6	*Saponaria officinalis*	30 kDa	Inhibiting tumor cells	Savino et al. (2000); Barthelemy et al. (1993)
Bouganin	*Bougainvillea spectabilis*	30 kDa	Ribosome inhibiting protein	Oglu et al. (1994); Jack et al. (2010)
Lychnin	*Lychnischalcedonica*	26 kDa	Ribosome inhibiting protein	Chambery et al. (2006)
Cinnamomin	*Cinnamomumcamphora*	30 kDa	Ribosome inhibiting protein	Liu et al. (2002)
Ricin	*Ricinus communis*	60–65 kDa	Ribosome inhibiting protein	Bellisola et al. (2004)
Tetramericlectins (Jacalin and Artocarpin)	*Artocarpus integrifolia*	66 kDa	Acts as an agglutinin	Barre et al. (2004)
Gelonin	*Geloniummultiflorum*	30 kDa	Ribosome inhibiting protein	Chemie (2004)

8. Putative mechanisms for anti-microbial, anti-viral and anti-tumor activities of seed storage proteins

Anti-microbial and anti-viral activities of seed storage proteins is gaining wide interest for usage in health and food industries. Putative mechanisms responsible for anti-microbial activity can be illustrated by ribosome-inactivating protein and agglutination reaction mechanisms (Table 4).

8.1. Ribosome-inactivating protein (RIPs)

Seed proteins that are having the capacity to either inhibit or reduce the protein translation *in vitro* by damaging the ribosomal subunit are termed as “ribosome inactivating proteins” (RIPs) (Walsh et al., 2013). Ricin, abrin and Shiga toxin (*Shigella dysenteriae*) are grouped as type II RIPs as they possess proteolytic processed active A-chain and B-chain linked by disulphide bonds. For example, Shiga family and ricin toxins inactivate 60S ribosomal subunits through N-glycosidic cleavage that release a specific adenine base from the sugar-phosphate backbone of 28S rRNA (Endo et al., 1988; May et al., 1989; Funatsu et al., 1991). The B-chain of seed protein is responsible for binding seed protein (ricin) to glycoproteins or glycolipids on the surface of tumor cells to promote endocytosis (Endo and Tsurugi, 1987). Pokeweed antiviral protein (PAP), gelonin (*Gelonium multiflorum*), β-luffin (*Luffa cylindrica*), trichosanthin (*Trichosanthes kirilowii*) and saporin (*Saponaria officinalis*) are categorized as type I RIPs because of having either active A-chain or B-chain (Tumer and Li, 2012). A-chain of RIP type I and RIP type II hold an exclusively single RNA N-glycosidase domain. The B-chain of type II contains galactose-specific lectin. Type III RIP have N-terminal RNA N-glycosidase domain linked covalently to C-terminal domain (Liu, 2017; Fabbrini et al., 2017). Most of the RIPs have 30 kDa (approx) in size and regarding toxicity type II RIP is highly toxic than RIP type I and RIP type III, respectively. These toxins (RIPs) are gaining great interest because of their potential use in cancer, which can be synthesized in conjunction with monoclonal antibodies and immunotoxins. In addition, trichosanthin a RIP has showed potential activity against -HIV-1-infected T cells and macrophages (Zhou et al., 1994; Tumer and Li., 2012; Verma et al., 2016). These RIPs activity can be attributed due to conserved glutamic residue nearer to conserved arginine amino acid that play an important role in the catalysis (Hovde et al., 1988; Bonness et al., 1994; Hamilton et al., 2016).

8.2. Agglutination and agglutinin

Agglutination occurs by interaction of specific antibody with specific antigenic compounds either directly or indirectly (antigenic components adsorbed to substratum) resulted in formation of cell clumps (Stavitsky, 1998). Antigens usually derived from polysaccharide antigens of microorganisms, extracts of bacterial vaccines, antigens of viruses and Rickettsia can be used in the indirect haemagglutination reaction (Haryanto, and Kamilah, 2017). Non-antibody substances like viruses, plant proteins, inorganic colloidal acids and bases, salts of heavy metals and basic proteins (protamines, histones) could agglutinate erythrocytes (Sharon and Lis, 1972). The process of agglutination inhibition can be made by interaction of soluble antigen capable of combining other sites of antibodies that hampers the binding properties of antibody:antigen and ultimately inhibits the agglutination of the particles (Mejía and Prisecaru, 2005).

One of the putative mechanisms of seed storage proteins for anti-viral activity is by agglutination reaction. Agglutinins (antibodies) are particles or substances that coagulate the antigens through antigen-binding interactions (Damme et al., 2003). In some instances, agglutinins may be referred to sugar-binding protein lectins (Roy et al., 2014), which transforms from fluid-like state to thickened-mass state (Guo, 2013). Similarly, when seed storage protein interacts with virus could trigger to form agglutination that inactivates the virus activity (Ho et al., 2009).

8.3. Anti-viral activity

The anti-viral activity of peptides was attributed either to the entry of the host cell (adsorption) or its effect on the envelope of a virus. The strategy mostly employed for anti-viral activity is due to interaction of a peptide either with the host or virus receptors which hampers the entry of the virus (Espitia et al., 2012). For instance, peptides interact directly with viral specific receptors of the host that inhibits the binding of virus to the cell membrane or intracellular binding (Jenssen et al., 2006). Another strategy involves electrostatic association of negatively charged cell surface compounds on mammalian surface such as glucosaminoglycans (GAG) with virus, proteins and enzymes, respectively (Kumar et al., 2017).

As the insects are looming large for resistance to the antibiotics, an ingeniousness approach is to find natural and eco-friendly molecules with same functions. It is an innovative technology for preservation of

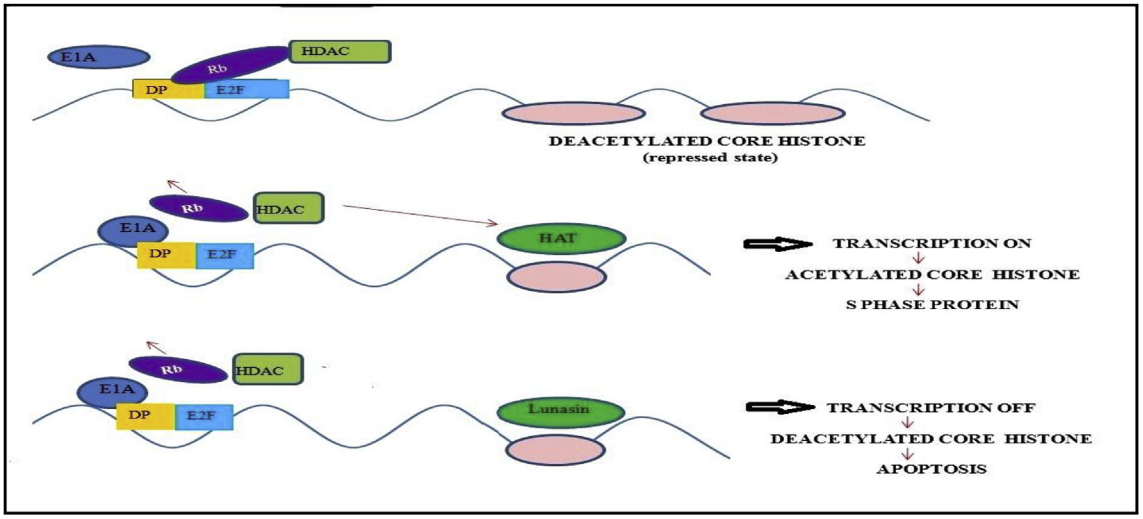

Fig. 3. Lunasin, a SSP selectively kills cells that are being transformed by disrupting the dynamics of histone acetylation-deacetylation cascade. The tumor suppressor protein (Rb) interacts with promoter (E2F) and engage histone deacetylase (HDAC) to remain the core histones in repression of transcription. The tumor suppressor protein (Rb) was inactivated by oncoprotein (E1A) and dissociates the Rb-HDAC complex from the core complex and presenting the deacetylated core histones for acetylation through histone acetyltransferases (HATs) to lead to tumor formation. Lunasin bind to the deacetylated core histones inhibiting HAT that ultimately suppress the transformed tumor cell and lead to cellapoptosis.

food aiming to reduce the microbial load before packing or prolongs the desired product. These anti-microbial natures of bioactive peptides have been envisaged to replace the conventional antibiotics.

8.4. Antitumor activity of seed storage protein

Several seed storage proteins such as lunasin, soymetide-4, oryzatensin, and soymetide-13 are predominantly reported for antitumor activity (Kumar et al., 2017). Lunasin derived from soybean have potential in prevention of mammalian cells tumor formation initiated by viral oncogenes (Hernández-Ledesma and Lumen, 2008) In the C3H and NIH3T3 cell lines, the tumor cell formation has been triggered by E1A factor (Fig. 3) through inactivation of tumor suppressor Rb protein and simultaneously acetylate core histones by histone acetyltransferases (HATs) (Lam et al., 2003; Hernández-Ledesma and De Lumen, 2008). Generally, tumor cell line is characterized by acetylation of core histones; whereas in normal cells the core histones are in deacetylated condition. Research studies have demonstrated that the lunasin administration is found to be effective in tumor suppression in C3H and NIH3T3 cells by inhibiting the binding of HAT enzyme with core histones and thus maintain the core histones in deacetylated form. Further, delay administration of Lunasin in C3H and NIH3T3 cells can also inhibit the developed transfection of tumor cell initiated by E1A gene (Lam et al., 2003). Further, Jeong et al. (2003) have revealed the effective efficiency of lunasin to suppress the tumor formation initiated by the ras-oncogene in MCF-7 cell lines.

Soymetides-4 is a seed storage protein derived from soybean and effective against the bacterial initiated tumor through the phagocytosis (Tsuruki et al., 2003). Oryzatensin, another seed storage protein derived from rice seed potential in antitumor activity via active phagocytosis. Horiguchi et al. (2005) have revealed importance of oryzatensin in autoimmune diseases, cancer and viral infection and further, the intensification of natural killer cells was noticed over administration with wheat hydrolysate. The fundamental mechanism of tumor formation inhibition by seed protein has been drafted in Fig. 3.

9. Seed storage proteins applications in food industry (active packaging)

The increasing resistance to antibiotics by pathogens has incited to look for novel compounds. An attractive approach is to replace the antibiotics with natural origin molecules such as peptides (Agarwal and Kumar, 2016). These peptides are having 1–50 amino acids with hydrophobic and cationic moieties that act as defense molecules for the host organism against fungi, bacteria, parasites and viruses (Sinha et al., 2016). Peptides with anti-microbial activity have potential applications in food processing unit, food preservation and biomedical applications. Hence, the mode of action of peptides pertaining to anti-microbial activity has been discussed for better understanding. Incorporation of antimicrobial peptides in food packaging is called as active packaging, which is envisaged to reduce the microbial contamination and enhance the product shelf life (Kumar et al., 2015).

9.1. Active packaging

Seed storage proteins are basically positive charged or amphipathic compounds that displayed quick, potentially long-term activity against spoiling protozoa, viruses, fungi and bacteria (Zasloff, 2002; Mulder et al., 2013). Active packaging is defined as per the European regulation (EC) No 450/2009 that active packaging consist of packaging systems, which interact with the stored food to “deliberately incorporate components that would release or absorb substances into or from the packaged food or the environment surrounding the food” (Espitia et al., 2012). Antimicrobial peptides can be packed by 3 ways: direct incorporation of peptide in the polymer, coating of peptides on the surface of polymer and immobilization of peptide in the polymer. The incorporated antimicrobial peptides diffuse from the packaging material to food and exert its biological role (Kumar et al., 2017).

Several researches have reported for the incorporation of antimicrobial peptides derived from seed directly in the polymeric material (bacteriocins). The bacteriocins peptides are resistant to heat and their antimicrobial activity is of great concern, when heating process is absent in food processing (Appendini and Hotchkiss, 2001). Seed storage peptides integrated in polymer films must be potential enough to diffuse over the packaging material for efficient action. Hence, polymers like cellulose acetate, alginate, chitosan, and soy protein have been greatly applied to develop films for direct integration of seed storage peptides (Marcos et al., 2008; Pires et al., 2008; Sivarooban et al., 2008; Santiago-Silva et al., 2009).

The antimicrobial activity of bacteriocins integrated into packaging polymer acts synergistically with other antimicrobial agents. Pranoto et al. (2005) have reported that synergistic activity was noticed for

nisin coupled with potassium sorbate and garlic oil over integration with chitosan films. Sivarooban et al. (2008) have revealed that soy protein films integrated with ethylenediaminetetraacetic acid (EDTA), nisin and grape seed extract exhibited inhibitory synergistic activity against *L. monocytogenes*, *E. coli* O157: H7, and *Salmonella typhimurium*. Enterocins A and B produced by *Enterococcus faecium* showed synergistic activity and inhibit the *L. monocytogenes* growth (Marcos et al., 2008).

Peptide coating on polymeric surfaces is another method, while the manufacturing of polymer needs tremendous processing conditions under high pressure (Appendini and Hotchkiss, 2002). The antimicrobial coating was done by ligating the film with or dipping the packaging film into the seed protein solution. For instance, linear low-density polyethylene (LLDPE) has been encrusted with lactocin 705 and lactocin AL705, a bacteriocins produced by *Lactobacillus curvatus* CRL705 having potential to inhibit the *Lactobacillus plantarum* CRL691 and *Listeria innocua* 7 (Massani et al., 2008). In another study, Scannell et al. (2000) have directly coated the polyethylene/polyamide in lacticin 3147 and nisin solution, which resulted polyethylene/polyamide with antagonistic effect against *L. innocua* and *S. aureus*.

Montesinos et al. (2016) have concluded from their studies that cecropin A found in rice seed as peptides are potential to inhibit the growth of microbial growth of *Dickeya dadantii* in food. Defensins rich in cysteine amino acids were extracted from *T. aestivum* and *Hordeum vulgare* and displayed insect amylase inhibiting activities (Wijaya et al., 2000; Stotz et al., 2009). Type I thionins (purothionins) are found in the grains of Poaceae family; while Type II thionins (α hordothionin and β-hordothionin) extracted from *P. pubera* leaves and nuts, respectively (Vernon, 1992). Both thionins, types I and II are reported to be active against the pathogens such as *Pseudomonas* sp., *Corynebacterium* sp., *Rhizoctonia* sp. and *Sclerotinia* sp. (Caleya et al., 1972; Oard et al., 2004; Giudici et al., 2004; Rayapuram et al., 2008).

10. Future perspectives

Millennium development goals (MDG) framed by the Food and Agriculture Organization (FAO) is aimed to alleviate poverty, of which supplementing nutritious protein is one of the important criteria, which need to be addressed to fulfill the goals. However, challenges like population explosion, shrinkage of natural resources, dearth of nutritious protein and climatic change have impeding to achieve MDG. Under these circumstances, supplementing seed storage protein in health diets and incorporating in food packages could help in boosting health conditions owing to their unique biological properties. Further, application of these SSP in active packages could enhance the shelf-life of the product and reduce the resistance of microbes significantly. Identifying the structures of SSP's shall envisage to synthesize artificially and can be utilized to fortify the foods.

11. Conclusions

Seed storage proteins serves as a major protein source and also for bioactive peptides, which are fragments of a protein with beneficial implications on human beings. It has gained paramount impetus, due to its manifold uses such as health benefits, antimicrobial, antiviral and antifungal activities. In plants the bioactive peptides are ubiquitous in distribution, which serves as a part of innate response upon elicitation. In addition, the bioactive peptides derived from plant source have structural similarity with the insect and animal sources. In most of the cases, mechanism of the bioactive peptides starts by binding the target membrane that results into permeabilization and rupture of the membrane. Recent research findings of the antimicrobial nature of peptides showed potent applications in the food industry. Increasing pathogens resistance due to wide use of antibiotics has heralded to emphasize on novel compounds with the similar functions. An ingeniousness approach is to find natural and eco-friendly molecules with same functions are desirable. Bioactive peptides with antimicrobial properties have been a potent alternative for its attributes. In addition, it can be incorporated into the packaging material that prolongs the food shelf-life.

Conflicts of interest

The author's declare that they have no conflict of interest.

Acknowledgements

Authors acknowledge the Director's of Indian Council of Agricultural Research –Indian Institute of Seed Science and National Bureau of Agriculturally Important Microorganisms for kind support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bcab.2019.01.044.

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