Heliyon 8 (2022) e10861

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

Transepithelial transport and cellular mechanisms of food-derived antioxidant peptides☆

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ARTICLE INFO

Keywords:
Antioxidants
Bioactive peptides
Transepithelial transport
Bioavailability
Cellular antioxidant activity
Molecular mechanisms

ABSTRACT

Considering the involvement of oxidative stress in the etiology of many non-communicable diseases, food-derived antioxidant peptides (FDAPs) are strong candidates for nutraceutical development for disease prevention and management. This paper reviews current evidence on the transepithelial transport and cellular mechanisms of antioxidant activities of FDAPs. Several FDAPs have multiple health benefits such as anti-inflammatory and anti-photoaging activities, in addition to antioxidant properties through which they protect cellular components from oxidative damage. Some FDAPs have been shown to permeate the intestinal epithelium, which could facilitate their bioavailability and physiological bioactivities. Molecular mechanisms of FDAPs include suppression of oxidative stress as evidenced by reduction in intracellular reactive oxygen species production, lipid peroxidation and apoptotic protein activation as well as increase in antioxidant defense mechanisms (enzymatic and non-enzymatic). Since many FDAPs have demonstrated promising antioxidant activity, future investigation should focus on further elucidation of molecular mechanisms and human studies to explore their practical application for the prevention and management of oxidative stress-related diseases.

1. Oxidative stress in health and disease, and the role of antioxidants

The human cells are constantly exposed to external sources of reactive oxygen species (ROS), such as air pollution, infective agents, UV radiation, and harmful chemicals including drug and alcohol overuse [1]. In addition, certain endogenous reactions (cytochrome P450 enzyme system, monoamine oxidase, xanthine oxidase and reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase catalyzed reaction) and mitochondrial oxidative phosphorylation produce ROS [2]. Furthermore, cells of the immune system also generate ROS in response to invasion by foreign bodies; however, hyperactive immune response produces excess ROS that may damage the host cells. ROS also include some free radicals with unpaired electrons, which render them unstable and reactive [3]. Hence, ROS can attack cellular components, such as lipids, proteins and nucleic acids, and abstract their electrons, thus initiating chain reactions. When the level of ROS exceeds the body's antioxidant defense capacity, it creates a systemic redox imbalance in favor of pro-oxidants, a condition known as oxidative stress [4]. Oxidative stress plays a key role in the initiation and progression of many diseases. For instance, oxidative stress has been linked to sickle cell anemia [5], skin diseases [6], malaria [7, 8], and gastrointestinal tract [9] and cardiovascular diseases [10]. In cancers, oxidation promotes mutation that induces resistance to apoptosis and initiation of tumorigenesis [11, 12, 13]. Similarly, hyperglycemia is associated with the glycation of cellular proteins to form advanced glycation end-products (AGEs), which promote oxidative stress and associated complications in type 2 diabetes [14, 15].

As a survival mechanism, living organisms, including plants and animals, have developed antioxidant systems to counteract the effects of ROS and free radicals, thus preventing cellular oxidative damages. The endogenous antioxidant system, including antioxidant enzymes (glutathione peroxidase [GPx], catalase [CAT], and superoxide dismutase [SOD]) and non-enzymatic antioxidants (e.g., reduced glutathione [GSH]), plays a major role in scavenging both external and endogenous ROS. However, to avoid systemic damage during oxidative stress, dietary antioxidants such as vitamins A, C and E, and phytochemicals are used to augment the endogenous antioxidants [16]. The role of antioxidants in the prevention and treatment of diseases cannot be overemphasized. Notably, FDAPs have gained the attention of scientists as natural

☆ This article is a part of the "Structure and function of food proteins and peptides"

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https://doi.org/10.1016/j.heliyon.2022.e10861
Received 5 November 2021; Received in revised form 23 April 2022; Accepted 27 September 2022

alternatives to synthetic antioxidants for health promotion [17, 18, 19, 20]. This review provides a comprehensive discussion on the intestinal transport and molecular mechanisms of FDAPs.

2. Overview of food-derived antioxidant peptides (FDAPs)

Antioxidant peptides are inactive within their parent protein structure but become active upon release via enzymatic, chemical hydrolysis or microbial fermentation. Several factors influence the antioxidant activities of food-derived peptides, including the parent protein source, amino acid composition, sequence, chain length, hydrophobicity, and preparation method such enzymatic and microbial hydrolysis [18, 21]. Different peptides with antioxidant properties have been produced from enzymatic hydrolysis of milk and plant proteins using a variety of proteases from plant, animal and microbial sources [22, 23, 24, 25, 26]. Notably, low molecular weight peptides (containing 2–15 amino acid residues) appear to be more bioaccessible and, hence, may potentiate better practical health-promoting effects *in vivo* [27, 28, 29, 30]. Most peptides with strong antioxidant properties possess acidic, hydrophobic and aromatic amino acid residues. Cysteine-rich peptides, and peptides with C-terminal tryptophan, proline and tyrosine, and N-terminal isoleucine, leucine, valine, alanine, phenylalanine and lysine are also generally known to exhibit antioxidant properties [31, 32, 33, 34]. Other antioxidant peptides have been reported to be resistant to mild changes in temperature, pH, and intestinal proteases [35, 36].

Several peptides from plant, animal and marine sources have been shown to exhibit potent antioxidant activities (Table 1). Chi et al. [37] isolated low molecular weight peptides (WEGPK, GPP and GVPLT) from bluefin leatherjacket head hydrolyzed with papain, and reported that the peptides demonstrated DPPH, hydroxyl ($^{\cdot}OH$) and superoxide ($^{\cdot}O_2$) scavenging activities, in addition to abrogation of ferrous-induced linoleic acid peroxidation. Similarly, a proline-rich oligopeptide isolated from *Lactococcus lactis* SL6-fermented bovine skim milk demonstrated radical scavenging potential, and the C-terminal proline proposed to play an important role in the antioxidant activity [38]. Using $^{\cdot}OH$ and $^{\cdot}O_2$ scavenging assays, peptides (CTN, HC, CGN, and CSGD) isolated from mung bean meal protein hydrolysate were shown to have antioxidant activities that were comparable to the effect of reduced glutathione [39]. Cysteine-containing peptides also show high antioxidant activities [31, 33, 40]. Endogenously, cysteine is a precursor of glutathione (a known antioxidant) and its thiol (-SH) group of cysteine also donates electron to quench free radicals. Peptides with C-terminal and N-terminal cysteine residues have also been reported to exhibit strong antioxidant properties [41, 42]. However, it not clear if these positions are major structural requirements for bioactivity. Tyrosine-containing peptides exhibit antioxidant activity by trapping free radicals and ROS in the phenolic group of tyrosine [43, 44]. Recently, antioxidant peptides derived from the enzymatic hydrolysis of proteins from *Porphyra haitanensis* (DKST) [45], blue mussel (PIIVYWK, TTANIEDRR, and FSVVPSPK) [46] and *Arthrospira platensis* (VTAGLVGGGAGK and PTGNPLSP) [47] demonstrated potent inhibitory effects against oxidative stress in cultured HepG2 hepatic cells. Also, fermented meat-derived antioxidant peptides were recently shown to protect DNA from oxidative damage in copper sulfate-phenanthroline-ascorbic acid-hydrogen peroxide-DNA chemiluminescence system [48], thus supporting the potential for further development of the FDAPs in the prevention and treatment of oxidative stress-related diseases.

Peptides are susceptible to structural changes during thermal and gastrointestinal processing, which may influence their antioxidant activities. Zhao et al. [49] reported that purple wheat bran-derived tripeptides with terminal cysteine residues (QAC and SSC) were functionally more thermostable, based on superoxide radical scavenging, than others (CGFPGHC, RNF and WF). This was unexpected as cysteine residue is susceptible to oxidation during thermal treatment. Previously, the other peptides (CGFPGHC, RNF and WF) were found to be more susceptible to degradation by pepsin, trypsin, or chymotrypsin, thereby reducing antioxidant activities [50]. Nonetheless, assessment of the structural stability of the peptides is needed to validate the proposed effect of these treatments. The presence of C-terminal proline residue is thought to increase the gastrointestinal stability of peptides, although the peptide chain length and absence of protease recognition and cleavage sites (scissile bonds) may be more important [51]. Generally, low molecular weight peptides (<1 kDa) rich in hydrophobic amino acids have been recorded to have potent antioxidant properties and are more biostable and bioavailable upon oral consumption [52, 53]. However, a comprehensive knowledge of the structural requirements to achieve combined biostability, bioavailability and bioactivity of FDAPs should be developed to facilitate their application as bioactive factors in nutraceuticals and functional foods.

3. Intestinal transport and potential bioavailability of FDAPs

To exhibit beneficial physiological effects, FDAPs must pass through the intestinal cell in their structurally intact form, resisting hydrolysis by gastrointestinal tract proteases and brush border peptidases. It is important to note that no mechanism of transport is specific for FDAPs; hence, FDAPs are transported using the same mechanisms as other bioactive peptides. Studies from our group and others [52, 54, 55, 56, 57, 58] have extensively discussed the current knowledge on the biostability, bioaccessibility and bioavailability of bioactive peptides. In this section, we provide an overview of unique characteristics of peptides that favour their transepithelial transport, giving examples using FDAPs. Transepithelial transport and routes of transport of peptides vary based on physicochemical properties, including net charge, hydrophobicity, chain length and sequence of the peptide [59]. Interestingly, the *in vivo* bioactivities of some peptides may be directly associated with their fragments generated by the action of proteases and peptidases during gastrointestinal digestion and intestinal transport. For more details on the effects of blood proteases and peptidases on peptide bioavailability, see the review by Segura-Campos et al. [60]. For example, the antioxidative peptide VLPVPQK from casein hydrolysates was reported to be hydrolyzed to VLPVPQ by Caco-2 cell peptidases, and both the native peptide and its fragment were transported across the cells by peptide transporter (PepT1) and sodium-coupled oligopeptide transporter (SOPT2) systems, and not by intracellular transcytosis [61]. In another transepithelial transport study in Caco-2 cells, some casein peptides were detected intact post-transport with half-lives of 14.26, 20.07 and 13.17 min, respectively for MPFPK, KEMPFPK, and KNQDKTEIPT [52]. Based on *in vitro* bioactivity, the transported peptides are strong candidates for further evaluation of antioxidant and LDL oxidation-inhibitory properties at the tissue levels *in vivo*.

Furthermore, using a Caco-2 cell monolayer co-culture with mucus-secreting goblet (HT29) cells, Xu et al. [62] proposed the mechanism of transport of antioxidant tripeptides (LKP and IQW) from egg white ovotransferrin to be mediated via PepT1 due to partial inhibition of transepithelial transport observed in the presence of a PepT1 competitive inhibitor. In addition to active transport *via* PepT1, the authors proposed a passive transport of the egg white peptides *via* the tight junctions. This finding is interesting because it highlights the possibility that the tripeptides permeated the mucus layer secreted by goblet cells prior to transepithelial transport. This important factor is lacking or underemphasized in most studies and may influence the bioaccessibility and bioavailability of FDAPs [51]. Generally, intestinal transport and the route of transport of FDAPs, especially *via* transcytosis, have been shown to depend on molecular weight, net charge and hydrophobicity of peptides [63], with small-sized, positively charged and hydrophobic peptides being generally more permeable than others. Nonetheless, there is currently no consensus on the structural requirements of FDAPs or peptides in general for transepithelial transport. This underscores the need for comprehensive structure-transport relationship studies using known bioavailable peptides and physiologically relevant intestinal models.

Table 1. Food-derived antioxidant peptides (FDAPs) from recent *in vitro* studies.

Peptide sequence	Source	Antioxidant assay	Reference
FDAPs from plant sources			
CGN, HC, SRSA, CTN, and CSGD; LLLGI, AIVIL and HADAD	Mung bean meal	DPPH, $^{\cdot}OH$ and $^{\cdot}O_2$ radical scavenging, metal ion chelating activities, and ferric reducing antioxidant power	[39, 109]
TSSSLNMAVRGGLTR and STTVGLGISMRSASVR	Finger millet	ABTS, DPPH and $^{\cdot}OH$ radical scavenging and metal ion chelating activities	[110]
CGFPGHC, QAC, RNF, SSC, and WF	Purple wheat bran	$^{\cdot}O_2$ radical scavenging and Trolox equivalent antioxidant capacity	[49]
GNPDIEHPE, TNDRPSIG, SVIKPPTDE, VIKPPTDE, GNPDIEHPET, LVPPQESQ, EITPEKNPQ, TLVNNDDRDS, NSQHPEL, FEEPQQPQ	Soybean flakes	ABTS, DPPH scavenging activities, ferric reducing antioxidant power, metal ion chelating capacity and inhibition of intracellular ROS generation	[111]
NL, QL, FL, HAL, AAVL, AKTVF and TPLTR	Wheat bran protein	Oxygen radical absorbance capacity	[24]
PGPIPN, PFPGPIPN, YPFPGPIP, VYPFPGPIPN, MPFPKYPVEP, EPVLGPVRGPFP, QEPVLGPVRGPFP, TPVVVPPFLQPE and TQTPVVVPPFLQPE	β-casein	DPPH and $^{\cdot}O_2$ radical scavenging capacity	[34]
IY, LY, VY, YLA, and MPS	Brown rice protein	Scavenged ROO and $ABTS^{+}$ radicals, chelates metal ions and inhibited oxidative stress in erythrocytes	[112, 113]
TVFDGELR, ADVFNPR, CAGVSAIR and LVYIIQGR	Palm kernel expeller glutelin-1 hydrolysates	$^{\cdot}OH$ radical scavenging activity	[114]
PQFYW and RPEIV	Coconut cake	$^{\cdot}OH$ radical scavenging activity	[115]
SDRDLLGPNNQYLPK	Pearl millet	DPPH, ABTS radical, $^{\cdot}OH$ radical scavenging, metal ion-chelating ability and reducing power	[116]
GY, PFE, YTR, FG, QY, IN, SF, SP, YFE, IY and LY	*Moringa oleifera* seeds	DPPH, and ABTS radicals scavenging	[117]
LTEIIP	Chickpea sprout	DPPH, and $^{\cdot}OH$ radicals scavenging	[118]
FDAPs from terrestrial animal sources			
YASGR	Chicken dark meat	Peroxyl radical scavenging activity	[119]
HTYHEVTKH and WPVLAYHF	Spotted babylon snail	ABTS and DPPH radicals scavenging activities	[120]
LTEQESGVPVMK	Ostrich egg white protein	DPPH, $^{\cdot}OH$ and $^{\cdot}O_2$ radicals scavenging, ferric reducing antioxidant power, metal ion-chelating and inhibition of linoleic acid autoxidation	[121]
DLEE	Dry-cured Xuanwei ham	DPPH, $^{\cdot}OH$ and $^{\cdot}O_2$ radicals scavenging activities	[122]
MVPYPQR	Camel milk	ABTS radical scavenging activity	[123]
AGPSIVH, FLLPH and LLCVAV	Duck breast	DPPH, and ABTS radicals scavenging and FRAP	[124]
QSLVSVPGMS	Hen egg-yolk	Strongly inhibited DPPH radical, moderately chelated metal ions, and strongly inhibited ACE activities	[125]
ITTNPYDY, IGWSPLGSL, ITTNPYDYHY, and LRVAPEEHPTL	Myofibrillar muscle of chicken breast	DPPH radicals scavenging, FRAP and inhibition of lipid peroxidation	[126]
FDAPs from marine sources			
GGPAGPAV, GPVA, PP and GF	Salmon gelatin	Oxygen radical absorbance capacity	[127]
YASVV, NFWWP, FWKVV, TWKVV and IRWWW	Miiuy croaker muscle	DPPH radical scavenging activities	[128]
ATSHH	Sandfish	DPPH radical scavenging capacity	[129]
VTAGLVGGGAGK and PTGNPLSP	*Arthrospira Platensis*	ABTS, and $^{\cdot}OH$ radical scavenging and metal ion-chelating activities	[47]
DKST	*Porphyra haitanensis*	DPPH radical scavenging capacity and inhibition of oxidative damage to HepG2 cells	[45]
PIIVYWK, TTANIEDRR, and FSVVPSPK	Blue mussel	DPPH radical scavenging and ORAC activities, and protected cultured cells from H_2O_2-induced hepatic damage	[46]
GAGLPGKRER	*Pinctada fucata* muscle	DPPH, $^{\cdot}OH$ and $^{\cdot}O_2$ radicals scavenging	[130]
FIMGPY, GPAGDY and IVAGPQ	Skate cartilage	DPPH, ABTS and $^{\cdot}OH$ radical scavenging, and inhibition of peroxidation of linoleic acid	[131]
FKGPACA and SVLGTGC	Silkworm pupae	ABTS radical scavenging activity	[132]
AGD	*Hippocampus abdominalis*	$^{\cdot}OH$ and $^{\cdot}O_2$ radicals scavenging activity *in vitro* and inhibition of cellular oxidative stress *in vivo*	[133]
ATVY	Black sharkskin	ABTS radical scavenging activity	[134]
HGPOGE, AGPKGH and MLGPYGPS	Skipjack Tuna scales	DPPH, $^{\cdot}OH$ and $^{\cdot}O_2$ radicals scavenging activities	[135]
KGYR	Round scad	DPPH, and $^{\cdot}OH$ radicals scavenging and FRAP	[136]
APLEEPSSPH, IREADIDGDGQVN, PEILPDGDHD and ASDEQDSVRL	Crucian carp	DPPH radical scavenging and ferrous chelating ability	[137]
VENAACTTNEECCEKK and VEGGAACTTGGEEGCCEKK	*Arca subcrenata*	DPPH, and ABTS radicals scavenging and FRAP	[138]
GPE, GARGPQ and GFTGPPGFNG	Scalloped hammerhead cartilage	DPPH, ABTS, $^{\cdot}OH$ and $^{\cdot}O_2$ radicals scavenging, and inhibition of peroxidation of linoleic acid	[139]

(*continued on next page*)

Table 1 (*continued*)

Peptide sequence	Source	Antioxidant assay	Reference
FYKWP, FTGMD, GFEPY, YLPYA, FPPYERRQ, GFYAA, FSGLR, FPYLRH, VPDDD, and GIEWA	Swim bladders of miiuy croaker	DPPH, $^{\cdot}OH$ and $^{\cdot}O_2$ radicals scavenging, and inhibition of peroxidation of linoleic acid	[140]
PELDW, WPDHW, FGYDWW, and YLHFW	Spanish mackerel muscle protein hydrolysates	DPPH, $^{\cdot}OH$ and $^{\cdot}O_2$ radicals scavenging, and inhibition of peroxidation of linoleic acid and H_2O_2-induced oxidative damage in plasmids	[141]

Abbreviations: 2,2′-azinobis (3-ethylbenzothiszoline-6-sulphonic acid) diammonium salt ($ABTS^{\cdot+}$); diphenyl-1-picrylhydrazyl (DPPH); hydroxyl radical ($^{\cdot}OH$); superoxide anion radical ($^{\cdot}O_2$); ferric reducing antioxidant power (FRAP); reactive oxygen species (ROS).

Despite their permeability across the intestinal epithelium, many bioactive peptides are not bioavailable in substantial amounts *in vivo*. Microbial fermented corn gluten meal containing short-chain oligopeptides were reported to suppress lipid peroxidation and enhance antioxidant enzyme activities in serum and liver tissues [64]. Although this may suggest that the FDAPs were absorbed, detection and quantification of the parent peptides in the serum and tissues are crucial to validating their biostability and bioavailability. Moreover, endogenously generated fragments of the dietary peptides could have been absorbed and contributed to the antioxidant activities. For instance, soybean-originated 43-residue peptide, lunasin, which showed chemopreventive cellular effects against oxidative stress [27], and its digestion fragment, RKQLQGVN, were reported to permeate Caco-2 cell monolayer by passive transport *via* paracellular tight junction permeability [28]. Based on the limited literature in this area, short chain hydrophobic peptides are hypothesized to be more resistant to hydrolysis by intestinal brush border proteases and to permeate the intestinal epithelium in their intact form [51, 63, 65]. Some peptides that are not absorbed through the intestine can also offer health benefits by protecting the intestine from oxidative damage; this topic has been extensively discussed in a recent review [66]. Aside their direct radical-scavenging properties, the peptides that are not bioavailable can stimulate the release of mucus to protect the mucosal cells of the intestine [67, 68, 69]. Unabsorbed bioactive peptides may also influence the gut microbiota population and metabolism in a way to generate a positive oxidative state. Future studies should consider establishing the role of gut microbiota on the antioxidant properties of unabsorbed FDAPs, considering that gut microbiota have been proposed to mediate other health-promoting effects of bioactive peptides [70, 71, 72].

4. Cellular mechanisms of action of FDAPs

FDAPs have been shown to elicit cellular antioxidant activities *via* specific proposed mechanisms, including upregulation of gene expression and activation of cytoprotective and antioxidant enzymes, and inhibition of intracellular ROS production and lipid peroxidation. These physiological events essentially follow the modulation of Keap1/Nrf2/ARE, PI3K/Akt/mTOR, NF-κB/MMPs and DAF-16 signaling pathways depending on the cells involved.

4.1. Activation of cytoprotective and antioxidant enzymes

Food protein hydrolysates and peptides have exhibited antioxidant activities *in vitro* and *in vivo* that are relevant in mitigating aberrant physiological processes and health conditions [73, 74]. For example, the aging process is linked with increased oxidative stress that damage important cellular structures [75, 76, 77]. In addition, premature aging has been associated with elevated generation of AGEs leading to increase in oxidative stress [78]). Experimentally, aging has been induced using D-galactose and muscarinic receptor blocker overload and exposure to UV radiation, leading to the formation of AGEs, inflammation and oxidative stress, which promote premature aging and memory loss [79, 80, 81]. In UV-radiation-generated mouse skin aging, Chen et al. [82] and Xu et al. [83] demonstrated that salmon skin gelatin and walnut protein hydrolysates dose-dependently abrogated UV-radiation generated skin photoaging in rats and mice. The hydrolysates acted by inhibiting matrix metalloproteinase-1 (MMP-1) activity and lipid peroxidation and elevating the antioxidant status and immune function. Two peptides, WSREEQEREE and ADIYTEEAGR, were found to retain the anti-photoaging properties of the walnut protein hydrolysates and they acted by downregulating gene expression of inflammatory cytokines (interleukins (IL)-1β and IL-6) and inhibiting MMP-1 activity and the phosphorylation of IκB and p-65 proteins, which are activators of the NF-κB/MMPs signaling pathway [83]. Similarly, pine nut-derived peptides (MQIFVK, MASVPTK, EMVELPLR and VVLIGDSGVGK) reduced D-galactose-induced premature aging in mice by suppressing lipid peroxidation and enhancing the activities of SOD and GPx in mouse serum, and heart and liver homogenates [84]. The ability to boost the activities of antioxidant enzymes (CAT, GSH, SOD and GPx) (Figure 1), inhibit lipid peroxidation (malondialdehyde [MDA]) and protein oxidation (protein carbonyl), and downregulate gene expression of MMPs in mice have been reported as the antioxidant mechanisms of other FDAPs in preventing UV radiation-induced skin photoaging [83, 85, 86, 87]. These biological properties show that FDAPs have future application in the development cosmeceuticals and nutraceuticals for the prevention and treatment of aging-related skin diseases.

Furthermore, FDAPs have been reported to modulate oxidant-induced elevation of the endogenous antioxidant system. For example, lunasin or its fragments showed chemopreventive effect by reducing the elevated activities of GPx and CAT, and protein carbonyl formation induced by tert-butylhydroperoxide [27]. Conversely, a dipeptide, FC, identified in the large subunit of plant and microalgae ribulose-1,5-bisphosphate carboxylase was reported to restore (at 5 μM peptide) and augment (at 10 μM peptide) the mRNA expression of SOD-1 and CAT in hydrogen peroxide-induced oxidative stress in cultured liver (HepG2) cells [88]. Interestingly, GSH levels were augmented in normal cells by the FDAPs treatments [27, 88]. These findings suggest a possible protective role of the FDAPs in normal cells or the presence of a condition/response that enhance endogenous GSH synthesis, e.g. the availability of cysteine residue in FC, which could serve as GSH precursor. As oxidants are expected to deplete endogenous antioxidants like GSH and activate the antioxidant enzymes, it is possible that the type and amount of oxidants and cells used, and duration of oxidant exposure affected the cellular responses and effect of the FDAPs. This highlights the need to establish physiologically relevant models with close simulation of the complex cellular environments under oxidative stress for specific disease and health conditions.

4.2. Inhibition of intracellular ROS production

Endotoxin or lipopolysaccharide (LPS) induces inflammation and oxidative stress by enhancing the activation of nuclear factor-kappa B (NF-κB), which translocates to the nucleus to activate iNOS gene and protein expression. Activation of NF-κB signaling pathway also leads to redox imbalance in favor of oxidative stress because it causes mitochondrial dysfunction leading to the alteration of cellular energy metabolism and increase in ROS production [89]. These processes are implicated in the pathogenesis of many diseases. FDAPs have shown the ability to inhibit

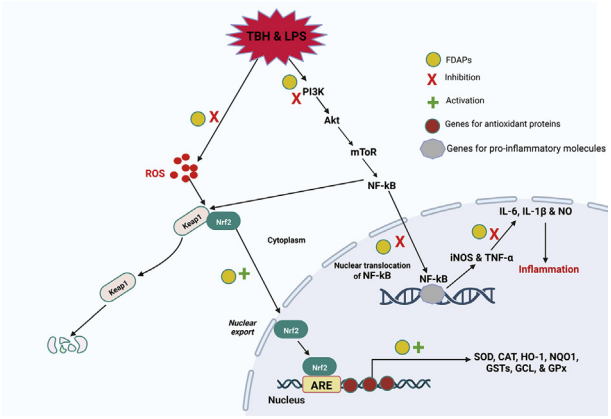

Figure 1. Cellular mechanisms of food-derived antioxidant peptides (FDAPs).

intracellular production of ROS. For example, soybean-derived antioxidant peptide fractions were reported to suppress intracellular ROS production, and reduced IL-1β, IL-6 and prostaglandins E2 levels in LPS-activated macrophage (RAW 264.7) cells via blocking of the NF-κB and iNOS pathways [90]. In tert-butyl hydroperoxide (TBH)- and LPS-induced injury and microglial activation in HMC3 microglial cells, *Salvia hispanica* protein hydrolysates produced with pepsin-pancreatin protected HMC3 microglial cells from oxidative damage by suppressing pro-inflammatory cytokines (TNF-α and IL-6) and intracellular ROS production [91] (Figure 1). Despite the promising bioactivity, there is no information on the specific cellular target that mediate the inhibition of ROS production by FDAPs. It is also not clear if these FDAPs acted by binding extracellular receptors to trigger the intracellular effects or after cellular uptake to interact directly with components of the ROS production pathways. Furthermore, the direct reducing capacity of the sulfhydryl group of dipeptide, FC, was proposed to play a role in its inhibitory effect against intracellular ROS [88]. Therefore, two mechanisms may be at play for the overall effect of FDAPs on ROS production, viz. direct antioxidant effect and regulation of intracellular antioxidant pathways. Some studies have reported physiological evidence to support the effects on ROS production. In mice treated with D-galactose, two FDAPs (FYY and DW) from fish protein hydrolysates suppressed lipid peroxidation in the brain, in addition to beneficial gene regulatory effects [92]. While these bioactivities make the FDAPs strong candidates for use as nutraceuticals, much is unknown about their intracellular targets, mechanisms of function and biological fate in tissues post-activity.

4.3. Activation of antioxidant system via oxidative signaling pathways

On oxidative stress, cells activate their antioxidant protection system, such as the activation of Keap1/Nrf2/ARE signaling pathway, leading to the upregulation of gene expression of antioxidant enzymes (NAD(P)H quinone oxidoreductase 1 (NQO1), heme oxygenase 1 (HO-1), glutamate-cysteine ligase (GCL) and glutathione-S-transferases (GSTs)) to protect the cells from oxidative damage and apoptosis [93]. Similar to oxidant-inducible mammalian Nrf2 transcription factors, DAF-16 and SKN-1 are two transcription regulators in *Caenorhabditis elegans* that mediate the expression of target genes, such as superoxide dismutase-3 (sod-3), heat shock proteins (hsp-6 and hsp-16.2) for DAF-16 and GSTs (gst-4 and gst-10) for SKN-1 [94, 95, 96]. The downstream effects of these proteins result in detoxification of oxidant species and cellular protection against oxidative damage. Several compounds target the oxidative signaling pathways as a mechanism for their antioxidant effects. Recently, antioxidant peptides (DVEDLEAGLAK and EITSLAPSTM) isolated from golden cuttlefish hydrolysates were reported to exhibit their cytoprotective effects against oxidant-induced cellular injury by inhibiting ROS formation and lipid peroxidation in high-fat *C. elegans* via upregulation of mRNA expression of sod-3, cat-1 and ctl-1 genes [54]. This result suggests that the peptides attenuated oxidative stress by activating the DAF-16 signaling pathway. Similarly, Zhao et al. [97] reported that two peptides AAVPSGASTGIYEALELR and NPLLEAFGNAK derived from purple sea urchin gonad hydrolysate alleviated paraquat-induced oxidative stress in *C. elegans* via the DAF-16 signaling pathway, by upregulating gene expression of sod-3 and hsp-16.2.

Furthermore, two hexapeptides (EAMAPK and AVPYPQ) derived from β-casein were shown to exhibit cellular antioxidant properties in H_2O_2-treated intestinal epithelial cells (IEC-6) via activation of Nrf2/ARE signaling pathway, leading to the upregulation of sod-3 mRNA expression [98]. When activated in response to oxidative challenge, the transcription factor Nrf2 binds to antioxidant response element (ARE) to upregulate mRNA expression of its regulatory genes, such as NQO1 and HO-1. NQO1 protects cells from quinones-induced oxidative damage and induction of mutation by detoxification of quinones and their metabolites to hydroquinones [99] whereas HO-1 protects cells by detoxifying heme into

Table 2. Recent studies on the cellular antioxidative activities and mechanisms of antioxidant protein hydrolysates.

Peptide/protein hydrolysate	Oxidative stress model	Cellular mechanism of action	Reference
Salmon skin gelatin hydrolysates	UV-radiation induced aging in mouse skin	Inhibited matrix metalloproteinase-1 (MMP-1) activity, improved antioxidant status (SOD, CAT and GPx activities) and reduced lipid peroxidation (malondialdehyde level) and activated collagen synthesis	[82]
Walnut protein hydrolysates	UV-radiation induced aging in mouse skin	Inhibited MMP-1 activity, increased SOD, CAT and GPx activities and reduced malondialdehyde level and activated collagen synthesis (elevated procollagen type I level)	[83]
GAGLPGKRER from *Pinctada fucata* protein hydrolysates	UV-radiation-induced mouse skin aging	Inhibited CAT, glutathione system and SOD activity, halted lipid peroxidation and suppressed UV-radiation-induced skin aging	[86, 130]
Silver carp skin hydrolysates	UV-radiation-induced mouse skin aging	Boosted antioxidant status, prevented protein oxidation and downregulating the gene expression of MMPs and halted lipid peroxidation	[142]
Whey protein hydrolysates	Normal Juvenile Arctic charr	Improvement in growth performance such as weight gain and feed consumption but a reduction in lipid peroxidation	[143]
Lunasin hysrolysates from soybean	Oxidative stress–induced vascular endothelial cell (VEC) injury and in ApoE deficient mice as well as azoximethane and dextran sodium sulphate-	Inhibited mitochondrial-dependent oxidative damage and endothelial apoptosis induced by H_2O_2 via suppression of Bax gene expression, release of cytochrome c and activities of caspases-3 and 9 while up-regulating Bcl-2 and HO-1 gene expression via PI3K/Akt/Nrf2/ARE pathway, and attenuated endothelial oxidative damage and atherogenesis in high fat	[101, 144]

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Table 2 (*continued*)

Peptide/protein hydrolysate	Oxidative stress model	Cellular mechanism of action	Reference
	induced hepatotoxicity in mice	fed ApoE-deficient mice. Inhibited chemically-induced oxidative damage on the hepatocytes of the mice and prevented histological changes	
Oat bran protein hydrolysates	Peroxide- and 2,2′-azobis(2-amidinopropane) dihydrochloride (AAPH)-stressed HepG2 cells	Improved cellular viability, reduced intracellular ROS generation, increased cellular GSH, GPx and SOD and inhibited apoptosis by reducing caspase-3 activity	[145]
Potato protein hydrolysates	H_2O_2-induced oxidative stress in C2C12 cells	Protected the cells from oxidative damage and increased the viability of the cells, by improving the antioxidant status	[146]
Casein and caseinophosphopeptide hydrolysates	AAPH and Fe^{2+}-induced cytotoxicity in human Caco-2, HT-29 and Saos-2 cells	Protected Caco-2/HT-29 cells in co-culture from AAPH and Fe^{2+}-induced cytotoxicity via metal chelating and antioxidant mechanisms and exhibited antioxidant effects by protecting human osteoblast (Saos-2) cells from AAPH-generated cytotoxicity	[22]
Coix seed protein hydrolysates	Alcohol-induced hepatic injury in ICR male mice	Increased alcohol metabolism by activating alcohol metabolic pathway and increased the activities of liver marker enzymes (AST and ALT) and SOD, attenuated inflammatory processes by suppressing serum tumor necrosis factor-α (TNF-α) and interleukin-β (IL-β) and abrogated lipid peroxidation as evidenced by reduction in MDA level.	[147]
Soybean protein hydrolysates	H_2O_2-induced oxidative stress in HepG2 cells	Salvaged cellular oxidative damage, inhibited ROS production, and reduced MDA level and oxidation of GSH, improved cellular ROS detoxification system by upregulating gene expression and protein level of Nrf2-ARE signal-responsive enzymes (SOD, CAT and GPx) and inhibited lipid peroxidation by reducing MDA level	[148]
Duck embryo eggs protein hydrolysates	H_2O_2-induced oxidative injury in HepG2	Protected the cells from oxidative assaults, prevented ROS production and lipid peroxidation and elevated antioxidant enzymes such as SOD, CAT and GPx	[149]
Blue mussel protein hydrolysates	H_2O_2-induced damage on Human umbilical vein endothelial cells (HUVECs)	Improved the viability of the cells and suppressed ROS release and lipid peroxidation, and elevated intracellular antioxidant status by increasing GSH, SOD, CAT and GPx levels in stressed cells via inhibition of caspace-3 activation and suppressed mRNA expression of apoptotic p53 and caspase-3 genes and reduced Bax/Bcl-2 ratio, suggesting the involvement of Nrf2-ARE and p53-Caspase-3 signaling pathways	[150]
Seahorse protein hydrolysates	H_2O_2-induced damage on Human umbilical vein endothelial cells (HUVECs)	Improved the viability of the cells and suppressed ROS release and lipid peroxidation, and elevated intracellular antioxidant status by increasing GSH, SOD, CAT and GPx levels in stressed cells via inhibition of caspace-3 activation and suppressed mRNA expression of apoptotic p53 and caspase-3 genes and reduced Bax/Bcl-2 ratio, suggesting the involvement of both Nrf2-ARE and p53-Caspase-3 signaling pathways	[151]
Krill protein hydrolysates	Alcohol-induced hepatic injury in mice	Increased body weight gain and survival rate, and antioxidant gene expression (SOD, CAT and GPx in hepatic tissues), and expression of transcription factors that promote antioxidant defense (Nrf2 and HO-1) while suppressing serum AST and ALT, and levels of hepatic cholesterol and gene expression of apoptotic proteins (caspase-3 and p53). The hydrolysates also attenuated hepatic tissue injury as evidenced by histological examination of alcohol injured mice liver treated with hydrolysates.	[152]
Whey protein hydrolysates	H_2O_2-induced oxidative stress in PC12 cells	Inhibited ROS generation, reduced calcium ion level and stabilized mitochondrial membrane potential of the cells. In addition, it increased the expression of Bcl-2 while suppressing that of Bax, and induced degradation of poly (ADP-ribose) polymerase (PARP) while antagonizing caspase-3 activation. In general, the materials protected PC12 cells from H_2O_2-induced oxidative damage	[153]
Nile tilapia skin gelatin hydrolysates	H_2O_2-induced oxidative injury in IPEC-J2 cells	Improved cellular viability and strengthened the cell membrane of IPEC-J2 cells but suppressed intracellular ROS formation, induced Nrf2 translocation from cytosol to nucleus and increased the expression and protein level of γ-glutamylcysteine ligase, and glutathione. Silencing of Pept1, Nrf2 or p62 diminished the cellular protective roles against oxidative damages, indicating that the mechanism of action is via activation of glutathione production and Pept1-p62-Nrf2 signaling pathway.	[154]

Table 3. Recent studies on the cellular mechanisms of action of identified FDAPs.

Peptide/protein hydrolysate	Oxidative stress model	Cellular mechanism of action	Ref
WSREEQEREE and ADIYTEEAGR from walnut protein	UV-radiation-induced mouse skin aging	Suppressed NF-κB signaling pathway by preventing the activation of IκB and p-65 proteins, downregulated gene expression of interleukins (IL)-1β and IL-6, inhibited MMP-1 activity and enhanced the expression of TGF-β and procollagen type I.	[155]
GAGLPGKRER from *Pinctada fucata* protein hydrolysates	UV-radiation-induced mouse skin aging	Inhibited CAT, glutathione system and SOD activities, halted lipid peroxidation and suppressed UV-radiation-induced skin aging	[86, 130]
PELDW, WPDHW, FGYDWW, and YLHFW isolated from Spanish Mackerel muscle	H_2O_2-generated plasmid DNA damage	Inhibited DNA damage by boosting the antioxidant status and preventing uncoiling and strand break	[156]
MQIFVK, MASVPTK, EMVELPLR and VVLIGDSGVGK derived from pine nut	H_2O_2-challenged HepG2 cells and D-galactose-induced premature aging in mouse	Improved the viability of HepG2 cells, and suppressed lipid peroxidation and enhanced antioxidant status by increasing SOD and GPx activity in mouse	[84]
LEPVIGT derived from porcine plasma	H_2O_2-induced oxidative stress in HepG2 cells	Protected HepG2 cells via Keap1-Nrf2-ARE signaling pathway	[103]
FYY and DW derived from lantern fish protein	D-galactose-induced aging	Suppressed lipid peroxidation level and expression of endothelial nitric oxide synthase, and improved memory impairment by elevating brain-derived neurotrophic factor	[92]
DVEDLEAGLAK and EITSLAPSTM from golden cuttlefish	High fat *Caenorhabditis elegans*	Prevented oxidative damage via upregulation of mRNA expression of DAF-16 signaling pathway-regulated genes (sod-3, catalase (cat-1) and ctl-1))	[54]
AYI, AYL, DREI and DREL from Jiuzao	2,2′-Azobis(2-methylpropanimidamidine)-stressed HepG2 cells	inhibited ROS generation, elevated SOD, CAT and GPx gene expression and improved the viability of HepG2 cells via Keap1-Nrf2-ARE signaling pathway	[102]
QDHCH from pine nut	Pulsed electric field-stressed and H_2O_2-induced oxidative stress in HepG2 cells	Improved antioxidant status (SOD, CAT, GPx and GSH-Rx), stabilized mitochondrial membrane potential and reduced lactate dehydrogenase (LDH) and malonaldehyde (MDA) levels as well inhibition of apoptosis by downregulating the gene expression of caspase-3	[84, 157]
VNP and YGD from Jiupei	1,1-Diphenyl-2-picrylhydrazyl, and 2,2′-azobis (2-methylpropionamide)-dihydrochloride-activated HepG2 cells	Improved intracellular enzymatic and nonenzymatic antioxidant defense system	[158]
FC from RuBisCO large subunit	H_2O_2-induced oxidative stress in Chang human hepatocytes	Prevented intracellular ROS generation and lipid peroxidation and increased intracellular GSH, CAT and SOD levels	[88]
ILGATIDNSK from defatted round scad	Heat shock and paraquat-generated oxidative stress and aging in *C. elegans*	Increased lifespan and activities of SOD and CAT, and reduced intracellular ROS level	[159]
Stable and resistant peptides (VENAACTTNEECCEKK and VEGGAACTTGGEEGCCEKK) from *Arca subcrenata*	Paraquat-generated oxidative stress and senescence in *C. elegans*	Extended the lifespan, improved age-related physiological decline in the nematode, and reduced fat and lipofuscin levels that accumulate in the nematode with age. The peptides also inhibited ROS generation and down-regulated *age-1* gene while upregulating oxidative stress-dependent genes (*mtl-1*, *sod-3*, *ctl-1* and *hsp16.2*) via DAF-16 signaling pathway	[138]
GLVYIL, YHNAPGLVYIL and DVNNNANQLEPR from oat protein	AAPH-generated oxidative stress in HepG2 cells	Protected cells by increasing cellular viability by antioxidant mechanisms, including inhibition of lipid peroxidation and elevation in SOD, CAT, GPx and GSH levels	[160]
SF and QY from *Moringa oleifera* seeds	H_2O_2-induced oxidative stress in Chang human hepatocytes	Protected Chang liver cells by reducing the levels of liver function enzymes such as aspartate aminotransferase (ALT) and alanine aminotransferase (AST) and lipid peroxidation marker, malondialdehyde (MDA) as well as boosting of levels of antioxidant enzymes (SOD and CAT), and preventing apoptosis of the cells.	[117]
ARHPHPHLSFM, AVPYPQR, NPYVPR and KVLPVPEK from milk	TBH-induced lipid peroxidation and H_2O_2-induced oxidative stress in Caco-2 cells	Scavenged ABTS radical and inhibited TBH-induced lipid peroxidation in Caco-2 cells. The peptides induced the translocation of Nrf2 from cytosol to nucleus, and prevented the interaction of Keap1 to Nrf2, allowing Nrf2 to bind to ARE, and activate the expression of genes that code for antioxidant and oxidants-detoxification enzymes (Trx1, TrxR1, GR, NQO1 and SOD1), suggesting that the mechanism of antioxidant effects of the peptides is via Keap1/Nrf2 signaling pathway.	[161, 162]
WGN, AW, RGWYE and GVPFW from mung bean	H_2O_2-induced oxidative stress in HepG2 cells	The peptides protected HepG2 cells from oxidative stress by increasing cellular viability via elevation in antioxidant status (CAT and GSH system) and inhibition of lipid peroxidation (MDA)	[163, 164]
ITTNPYDY and IGWSPLGSL from Myofibrillar protein of chicken breast	H_2O_2-induced oxidative stress in NIH-3T3 cells	Increased the viability of NIH-3T3 cells, inhibited intracellular ROS and lipid peroxidation in H_2O_2-induced oxidative stress in NIH-3T3 cells and improved intracellular glutathione concentration and SOD, CAT, GPx and GSH-Tx activities, and prevented apoptosis via	[126]

(*continued on next page*)

Table 3 (*continued*)

Peptide/protein hydrolysate	Oxidative stress model	Cellular mechanism of action	Ref
		inhibition of caspase-3 activation suggesting that the peptides have both antioxidant and cellular protective properties	
GLLLPH from corn gluten meal	H_2O_2-induced oxidative stress in HepG2 cells	Enhanced cell viability, inhibited intracellular ROS generation and lipid peroxidation and improved the expression of antioxidant status (SOD, CAT, GSH-Rx, GSH)	[165]
EKWAP, EDGPIPP, EARPPHPPIPP, and EARPPHPPIPPAP	H_2O_2-induced damage on SH-SY5Y cells	Increased viability of cells, restored altered mitochondrial membrane permeability, suppressed ROS generation, NO production and lipid peroxidation, all of which suggest antioxidant protection against oxidative stress	[166]
GPA from fish skin gelatin protein hydrolysate	H_2O_2-induced oxidative injury in IPEC-J2 cells	Enhanced ARE-luciferase activity to increase the gene expression and protein level of ARE-dependent antioxidant enzymes as well as reducing cellular ROS generation	[154]
YPLPSY from *Allium tuberosum*	H_2O_2-induced oxidative injury in HEK293T cells	Halted intracellular ROS generation, promoted stressed-cell survival and elevated the gene expression of PI3K, Akt, phospho-Akt, mTOR, phospho-mTOR indicating that the cellular protective mechanism is mediated via PI3K/Akt/mTOR signaling pathway	[167]
VRP, LKY, VRY and VVHPKES from Spent hens	Tumor necrosis factor alpha (TNFα) and angiotensin (Ang) II-induced oxidative stress in vascular smooth muscle A7r5 cells (VSMCs) and endothelial EA.hy926 cells (ECs)	Ameliorated oxidative stress by increasing the expression of antioxidant enzymes (GPx4 and SOD2) and suppressing in ROS generation	[168]

biliverdin/bilirubin [100]. In a follow-up study, Gu et al. [101] showed that lunasin protected EA.hy926 human umbilical vein endothelial cells against H_2O_2-induced intracellular cellular oxidative injury and mitochondria-associated endothelial apoptosis via suppression of Bax gene expression, release of cytochrome c and activation of apoptotic proteins (caspases-3 and 9). The peptide also up-regulated gene expression of tumor suppressor gene (Bcl-2) and HO-1 via the PI3K/Akt/mTor//Nrf2/ARE pathway, and reduced oxidant-mediated ROS production in endothelial cells, leading to the amelioration of endothelial oxidative damage and atherogenesis in high fat fed ApoE-deficient mice (Figure 1). Several other FDAPs (AYI, AYL, DREI, DREL, MQIFVK, MASVPTK, EMVELPLR, VVLIGDSGVGK and LEPVIGT) were recently demonstrated to protect HepG2 cells via the Keap1/Nrf2/ARE signaling pathway, leading to the upregulation of gene expression of antioxidant enzymes and ROS detoxification pathways [84, 102, 103]. Similar mechanisms were demonstrated by a dipeptide (IF) from potato protein hydrolysates in hypertension-generated ROS-induced renal damage in rats [104]. Tables 2 and 3 show other food-derived protein hydrolysates and peptides, respectively, that elicit their cellular antioxidative action via oxidant signaling pathways, and Figure 1 summarizes the cellular mechanisms of FDAPs.

5. Commercialization of FDAPs

Majority of the commercially available food protein and peptide-based products, sold as nutraceuticals or supplements, target mostly hypertension, obesity, and diabetes, with little attention given to oxidative stress. Examples of the products include Nutripeptin®, Fortidium®, Peptibal®, Stabilium®, Protizen®, Seacure®, Vasotensin®, Lapis support/Valtyron®, PeptACE®, and Levenorm® from marine sources; Calpis, Biozate, Lactium®, Evolus, and BiopureGMP from dairy sources; and LunaRich® X and PeptAIde from plant sources (see reviews [105, 106] for more information). Notably, LunaRich® X, a concentrated form of lunasin, a FDAP, is currently marketed by Reliv (USA) as a dietary supplement for lowering cholesterol [105]. Despite the large body of evidence on the antioxidant properties of peptides from vegetal sources, plant-derived antioxidant peptides are the least commercialized. This may be associated with high cost of production, and other general limitations in translating research on bioactive peptides such as lack significant health benefits from clinical studies. Additional limitations could be attributed to poor bioavailability and lack of in-depth knowledge of the pharmacokinetics of bioactive peptides, which are needed for approval prior to commercialization, as discussed in previous reviews [106, 107]. Furthermore, FDAPs have other potential applications, e.g. as cosmeceuticals and food preservatives against oxidative deterioration of food products; see the review by Sohaib et al. [108] for more details.

6. Conclusion and future directions

Due to safety concerns associated with synthetic antioxidants, natural compounds such as FDAPs are increasingly explored as safer and sustainable alternatives. Several studies have shown that food protein-derived peptides from animal, plant, microbial and marine sources have antioxidant properties. Thus, FDAPs have promising application against oxidation-induced cellular damage and the initiation and progression of associated diseases, such as cancer, atherosclerosis, neurodegenerative diseases and diabetes. FDAPs have demonstrated their antioxidant properties via three distinct mechanisms: (1) activation of antioxidant enzymes, (2) inhibition of intracellular ROS production, and (3) activation of antioxidant system via oxidative signaling pathways. Based on cellular studies, some peptides permeate the intestinal epithelium in their intact form, which could facilitate circulation, interaction with their target cells and elicitation of their antioxidant activities. However, future studies are needed to fill some important gaps. First, there is a need for strong physiological evidence on the bioavailability of dietary FDAPs in target tissues, beyond the cellular uptake studies. Second, the specific molecular targets of FDAPs need to be identified for better understanding of their structure-function relationships. Absorption and bioavailability of dietary FDAPs, especially those with multiple antioxidant mechanisms, are crucial in building evidence for future human studies and for application of FDAPs as nutraceuticals for improving human health and wellbeing.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability statement

No data was used for the research described in the article.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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