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Intestinal polyphenol antioxidant activity involves redox signaling mechanisms facilitated by aquaporin activity

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ABSTRACT

Ascertaining whether dietary polyphenols evoke an antioxidant or prooxidant activity, which translates to a functional role required to maintain intestinal cell homeostasis continues to be an active and controversial area of research for food chemists and biochemists alike. We have proposed that the paradoxical function of polyphenols to autoxidize to generate H_2O_2 is a required first step in the capacity of some plant phenolics to function as intracellular antioxidants. This is based on the fact that cell redox homeostasis is achieved by a balance between H_2O_2 formation and subsequent outcomes of antioxidant systems function. Maintaining optimal extracellular and intracellular H_2O_2 concentrations is required for cell survival, since low levels are important to upregulate endogenous antioxidant capacity; whereas, concentrations that go beyond homeostatic control typically result in an inflammatory response, growth arrest, or eventual cell death.

Aquaporins (AQPs) are a family of water channel membrane proteins that facilitate cellular transportation of water and other small molecule-derived solutes, such as H_2O_2, in all organisms. In the intestine, AQPs act as gatekeepers to regulate intracellular uptake of H_2O_2, generated from extracellular polyphenol autoxidation, thus enabling an intracellular cell signaling responses to mitigate onset of oxidative stress and intestinal inflammation.

In this review, we highlight the potential role of AQPs to control important underlying mechanisms that define downstream regulation of intestinal redox homeostasis, specifically. It has been established that polyphenols that undergo oxidation to the quinone form, resulting in subsequent adduction to a thiol group on Keap1-Nrf2 complex, trigger Nrf2 activation and a cascade of indirect intracellular antioxidant effects. Here, we propose a similar mechanism that involves H_2O_2 generated from specific dietary polyphenols with a predisposition to undergo autoxidation. The ultimate bioactivity is regulated and expressed by AQP membrane function and thus, by extension, represents expression of an intracellular antioxidant chemoprotection mechanism.

1. Introduction

The gastrointestinal tract has important roles to restrict and enable passive nutrient and non-nutrient uptake that results in bioavailability, while also enabling protection against potentially toxic xenobiotic compounds which can initiate systemic injury at cellular and organ levels [1]. Widely distributed in both proximal (e.g., small and distal (e.g., large) intestinal epithelia are a family of water channel membrane proteins, termed aquaporins (AQPs) [2,3]. For example, aquaporin 3 proteins (e.g., AQP3) with a molecular weight of approximately 30kDA [4–7] function to balance water and electrolyte absorption and secretion for the maintenance of intestinal cell migration and proliferation. These membrane proteins also act as a barrier to protect against exposure to dietary toxins [8–10]. Alterations in both acute- or long-term regulation of AQP3 leads to changes in both post-translational or post-transcriptional events required for optimal epithelial physiological function. For example, a disruption of the cellular redox balance initiates common intestinal disorders that include constipation or diarrhea [6,11], both of which underlie the loss of epithelial tight junction integrity and permeability initiated by the onset of inflammatory conditions [12,13]. Moreover, diverse stimuli ranging from hormonal to cytokine mediators affect intestinal AQP expression and function [14].

The intestinal lumen is the site for a vast number of endogenous stimuli that regulate AQP expression. AQP isomers have important roles

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to facilitate intracellular uptake of small molecules, such as H_2O_2, across cell membranes [15–17]. The gut microbiome can also affect AQP expression to an extent that affects bioavailability of oral drugs [18]. Hydrogen peroxide derived from extracellular prooxidation polyphenol reaction in small intestine, or alternatively from the gut microbiome, (e.g., probiotic *Lactobacillius acidopilus*) in the large intestine is recognized as a key metabolite for signaling intracellular redox reactions. Diffusion of H_2O_2 across membranes is compatible with its role as a signaling molecule; hence intracellular influx is required for H_2O_2 functioning as a second messenger to regulate, or modulate, important cell signaling pathways critical for cell homeostasis and proliferation [19]. Cytoplasmic concentrations of intestinal H_2O_2 are considered to represent a product of influx capacity and its production, minus the extent that it is scavenged or lost by efflux. Hence, the regulation of extracellular H_2O_2 production, in concert with intracellular mechanisms for molecule transport, is important to ensure intestinal redox homeostasis [20]. The physiological significance of AQP function therefore concerns the accepted view that AQPs are involved in increasing epithelial membrane permeability for H_2O_2, which is vital for regulating optimal intracellular H_2O_2 uptake. The end result for cell viability involves cell signaling to control against oxidative stress [21] and induced cytoprotective mechanisms that involve apoptosis and cell proliferation [22]. A strong example is the finding that AQP9 functions to modify early stages of LPS-induced endotoxic shock by facilitating uptake of extracellular H_2O_2 and triggering the NF-κB pathway [23].

It is important to recognize that both the quality and diversity of the human diet are very important to ensure optimal human intestinal health [24,25]. Polyphenols are recognized as extra-nutrients and bioactive biomolecules derived from fruits, vegetables and common tea and coffee beverages with the capacity to modify intestinal redox status and oxidative stress [26]. Polyphenols, when oxidized to quinone metabolites represent redox cycling compounds that can undergo repeated oxidation and reduction reactions and participate in Michael addition reactions with cysteine residues on Keap1 [27,28]. This interaction leads to the release, or activation of Nrf2, which subsequently upregulates the expression of intracellular antioxidant enzymes and detoxification proteins [29,30]. On the other hand, H_2O_2 generated by extracellular polyphenols oxidation also plays a significant role in Nrf2 activation [31]. This is a crucial mechanism by which polyphenols contribute to cellular defense against oxidative stress. The purpose of this review is to provide new perspectives on the importance of dietary polyphenols that participate with intestinal AQP activity, leading to optimal intestinal redox balance critical for human health.

2. Role of AQPs on maintenance of epithelial cell functionality

The human intestine is the largest immune organ system in the body and consists of a wide variety of cells derived from both non-hemopoietic (epithelial cells, goblet cells, Paneth cells), and hemopoietic origins (dendritic cells, macrophages, T-cells) [32,33]. Located on the apical membrane of intestinal epithelial cells are nine distinct AQP isoforms with various functions associated with transporters of water and small molecular weight solutes (Fig. 1 [4,5,7,34]. Basically, AQPs are regarded as diffusion facilitators for non-charged and partially polar solutes, including NH_3, urea, polyols and H_2O_2. Hydrogen peroxide being a substrate for aquaporin activity is largely a result of its physico-chemical properties, as it has a dipole moment that resists simple diffusion through a hydrophobic lipid bilayer.

Most importantly, AQP1, AQP3, AQP7 and AQP10 are expressed in the small intestine, whereas isoforms AQP1, AQP3, AQP7, and AQP8 are abundantly expressed in the colon [6,35–38]. AQP9 on the other hand is mostly expressed in hepatic tissue with a similar role that is important for general redox balance and inflammation [39]. To prevent overproduction of H_2O_2, AQP8 has a role to transport it for detoxification by catalase activity. The complexity of AQP function is best appreciated by the fact that some mechanisms of gating, a term used to describe the transport mechanisms and offered by different AQPs, are in fact shared by different AQPs. This enables an additional layer of regulation in AQP facilitated transmembrane transport when responding to stress. A summary of each type of AQP that is expressed in specific regions of both the small and large intestine is presented in Table 1.

Normal AQP expression is essential to regulate intestinal water transport, in contrast to abnormal expression of AQPs, which leads to a disruption of a Na^+/K^+ flux and subsequent gastrointestinal disorders

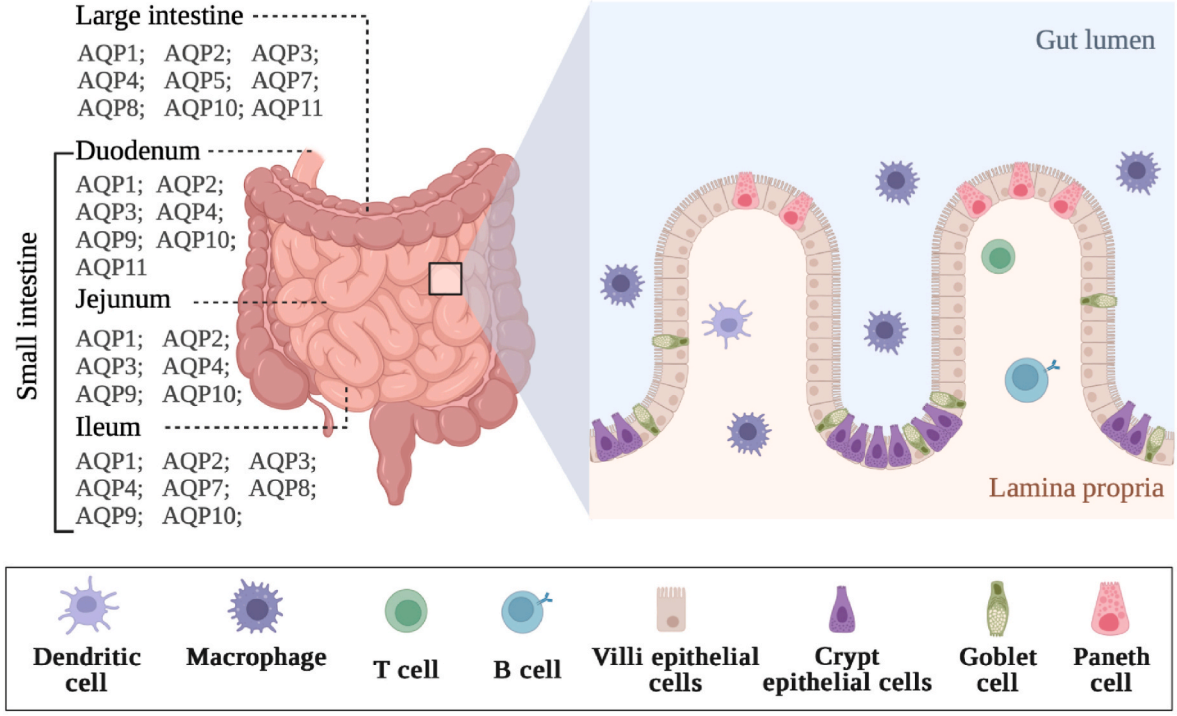

Fig. 1. Expression of AQPs with specific target cells in human gut lumen that facilitate gut homeostasis. Compiled from reports by Refs. [7,12].

Table 1
Expression of distinct AQP isomers in different type of cells in the human intestine[a].

Location	Cell type	Aquaporin	References
Small intestine	Villi epithelial cells	AQP3, AQP7, AQP8, AQP10	[5,40,41]
	Crypt epithelial cells	AQP3, AQP4	[5,40]
	Goblet cell	AQP3, AQP9, AQP10	[41,42]
	Paneth cell	AQP3	[41]
	Microvessels	AQP1, AQP10	[5,41]
Large intestine	Villi epithelial cells	AQP2, AQP3, AQP4, AQP7	[5,40] [35]
		AQP8, AQP10	[43,44] [45]
	Crypt epithelial cells	AQP7, AQP8	[5,46]
	Microvessels	AQP1	[5]
Lamina propria	Blood leukocytes	AQP1, AQP9	[47,48]
	Dendritic cell	AQP3, AQP5	[49]
	Macrophage	AQP1, AQP3, AQP5, AQP9	[50–52]
	T cell (Activated)	AQP1, AQP3, AQP5	[49]
	B cell (Activated)	AQP1, AQP3, AQP5	[49]

[a] Adapted from Refs. [6,53]; AQP 1, 2, 4, 5 and 6 are water transporters; AQP 3, 7, 8, 9, 10 & 11 are water and small solute transporters [34,42].

that include diarrhea or constipation [54] ()(Table 2). Of particular importance is the observation that abnormal expression of AQPs occurs in Crohn's, Ulcerative and Collagenous diseases in humans [35].

3. Hydrogen peroxide production and cell signaling

Hydrogen peroxide, when present in the intestine at low, controlled production and optimal cellular uptake, represents an essential second messenger involved in kinase signaling, compared to when it is present at high concentrations where it becomes toxic to the cell. Hydrogen peroxide is generated both extracellularly and intracellularly. One of the primary sources of extracellular H_2O_2 involves enzymatic reactions with specific enzymes, including NADPH oxidase [62]. The human gastrointestinal tract also contains a diverse population of bacteria that have the ability to produce hydrogen peroxide as a byproduct of metabolism [63,64]. Intracellularly, H_2O_2 can be generated from mitochondria, peroxisomes, intracellular-facing NADPH oxidase and cytochrome P450 reductases, where electrons escape from the electron transport chain, leading to the formation of superoxide ions. The superoxide ions are subsequently dismutated into H_2O_2 by superoxide dismutase enzyme (SOD). In addition, redox cycling compounds also have the capacity to generate H_2O_2 intracellularly as a byproduct of redox reactions. Redox cycling compounds transfer electrons to molecular oxygen, leading to the formation of superoxide ions, which are subsequently dismutated to H_2O_2 [65,66]. The generation of H_2O_2 from both intracellular and extracellular has significant implications in various biological processes.

Table 2
Summary of different reports on changes in aquaporin expression related to specific examples of intestinal disorders and disease in animal and human studies.[a].

Intestinal disease	Model	Aquaporin expression	References
Escherichia coli -induced diarrhea	Mice	AQP3 decreases	[36]
Escherichia coli- induced diarrhea	Piglets	AQP3, 11 decreases	[55]
Antibiotic-associated diarrhea	Rat	AQP3, 4, 8 decreases	[56]
Bile acid-induced diarrhea	Rat	AQP3, 7, 8 decreases	[57]
Irritable bowel syndrome	Rat	AQP1, 3, 8 decreases	[58]
Constipation	Mice	AQP3 increases	[59]
DSS induced colitis[b]	Murine	AQP4, 8 decreases	[46]
TNBS-induced colitis	Rat	AQP3, 8 decreases	[60]
Crohn's diseases	Human	AQP1, 3 decreases	[35]
Ulcerative colitis	Human	AQP7, 8 decreases	[35]
Collagenous colitis	Human	AQP8 decreases	[61]

[a] Expression of different AQPs were made using mRNA and/or protein techniques.
[b] Induction was done using DSS: dextran sulfate sodium; TNBS: 2,4,6-trinitrobenzene sulfonic acid.

At physiological levels, H_2O_2 is unreactive with most biological molecules due to a high activation energy barrier that includes reactions with thiol proteins and glutathione peroxidase and peroxiredoxin activities [67] that neutralize its activity. Intracellular H_2O_2 is removed non-enzymatically by antioxidant enzymes, including catalase, glutathione peroxidases, and peroxiredoxin. Whereas SOD is located in mitochondrial, cytosolic and extracellular spaces, respectively, catalase is mainly located in the peroxisomes, and glutathione peroxidases and peroxiredoxins are present in different cell compartments; the collective action of these enzymes is to prevent an increase or accumulation of H_2O_2 in specific cell compartments [68]. In addition, the normal expression of intestinal AQPs facilitates the entrance of H_2O_2 originating from extracellular to intracellular space, thus enabling the subsequent removal of reactive oxygen species (ROS) by post-transcriptional regulation of gene expression of intracellular antioxidant enzymes. This constitutes the important role of AQPs to control cellular efflux of H_2O_2 for optimal metabolic homeostasis. It also raises the question: should AQP function be considered when defining the antioxidant capacity of plant polyphenols that are predisposed to autoxidation and produce H_2O_2, a precursor for the intracellular uptake of this signaling molecule.

One example of this is the key mechanism for H_2O_2 to protect against exposure to oxidative stress through its interaction with a constitutive Keap1 (Kelch-like ECH-associated protein 1-E3 ligase) complex. This in turn targets the transcription factor Nrf2 (NF-E2-related factor 2) for proteasome degradation [69]. Exposure of the cell to H_2O_2, coincides with suppression of Nrf2 ubiquitination and the release of Nrf2 from cysteine rich residue clusters positioned on Keap1; the result being the stabilization of Nrf2, followed by its accumulation and nuclear translocation [70]. By diminishing Keap1 function, Nrf2 will accumulate in the nucleus, where it triggers the upregulation of antioxidant gene expression [70]. Hence H_2O_2 is a key electrophile for Nrf2 *de novo* synthesis, proposed to prepare the cell from an oxidative stress by

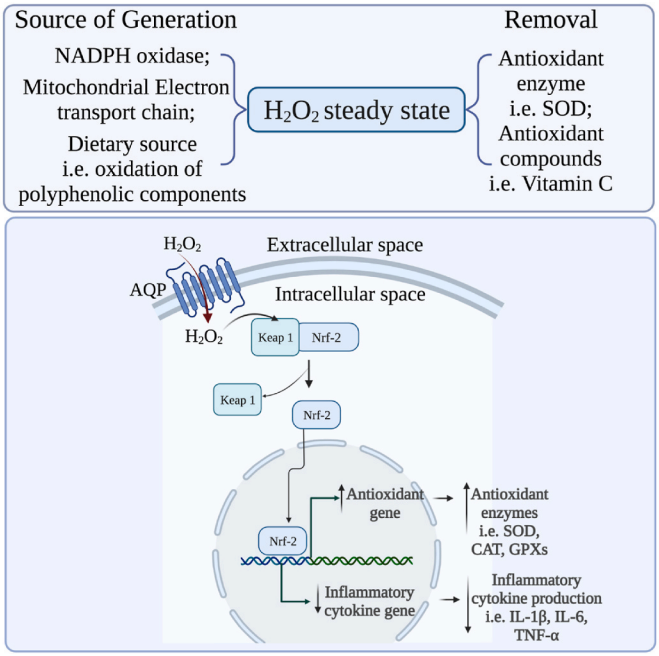

Fig. 2. Scheme describing aquaporin facilitated H_2O_2 entrance and downstream Nrf2 cell signaling to regulate antioxidant enzyme activity and reduce cytokine production in preparation for oxidative stress and inflammation.

facilitating a fail-safe response mechanism that involves interaction with Keap1 to remove ubiquitination and repression of Nrf2 activity (Fig. 2) [69,70]. Studies performed with different chlorogenic isomers have demonstrated the capacity to increase Nrf2 signaling in differentiated Caco-2 cells which lead to upregulated expression of target genes, that included glutathione peroxidases (GPXs) [26]. The capacity of phenolic acids to generate H_2O_2 via autoxidation is structure-specific and correlated with the level of Nrf2 cell signaling. This has been shown for gallic acid, where H_2O_2 generated by autoxidation triggered Keap1-Nrf2 activity, and when in the presence of catalase to remove H_2O_2, the reaction was lost [17]. This mechanism shown in cell culture studies has been extended to animal experiments with pigs, where chlorogenic acid prevented mucosal disruption and enhanced intestinal barrier integrity [71].

4. Aquaporin facilitated H_2O_2 diffusion and downstream cell functionality

Physicochemical and experimental evidence has shown that the transportation of H_2O_2 and the subsequent transmission of intestinal transmembrane redox signaling processes *in vitro* involves AQPs [17]. Passive diffusion of H_2O_2 across biological membranes requires specific aquaporin isoforms and associated roles in H_2O_2 diffusion in all mammalian cells [21,72–76]. A list of several AQPs in mammalian cells, in addition to intestinal cells, shown to be involved in transmembrane diffusion of H_2O_2, include: AQP1 [76], AQP3 [75] and AQP8 [73], and AQP9 [77]. Specifically, AQP3, AQP8 and AQP9 in human cells are involved in the transmembrane diffusion of H_2O_2 [73,75,77] (Table 3), which parallels important roles in the regulation of redox balance and implications for oxidative stress and associated inflammatory conditions. Functionality of AQPs is attributed to specific intermolecular structures, referred to as an aromatic/arginine selectivity filter, which selectively filters water and solutes [78,79]. The two-conserved asparagine-proline-alanine motifs allow the passage of charged ions via pores to be controlled [80–82]. Initial theories suggested that H_2O_2 crosses membranes freely by passive, non-protein-facilitated diffusion; however, this has been refuted by observing the presence of a H_2O_2 gradient across membranes of many different mammalian cell lines [83,84], collectively confirming roles for AQPs to regulate H_2O_2 transportation. AQPs also facilitate the transmembrane diffusion of water, unlikely achieved by non-facilitated, free diffusion across biological membranes [85]. However, although H_2O_2 and water share similar physicochemical features, the diffusion of H_2O_2 is relatively less efficient compared to water, therefore requiring a more active regulation towards H_2O_2 permeability across the membrane that is facilitated by AQPs.

The downstream redox-dependent signaling from AQP facilitated uptake of extracellular H_2O_2 is dependent on signal transduction pathways that are initiated at the binding of membrane receptors to corresponding ligands [103,104]. Of particular importance are the results that show H_2O_2 can also regulate the expression of H_2O_2 channels, leading to the conclusion that integrated regulation of AQP expression by H_2O_2 and the capacity to transport H_2O_2 are coupled in defining the cell response to H_2O_2 [21,105]. A scheme showing differentiated Caco-2 intestinal cell responses with cell migration and wound healing, characterized as an AQP3-H_2O_2-dependent response [86] is shown in Fig. 3.

Table 3
AQPs isomers facilitating the membrane diffusion of H_2O_2 in human cells.

AQP	Cell Type	AQP localization	Functionality	References
AQP3	HEK293 cells	Plasma membrane	Cell signaling	[21]
	HeLa cells	Plasma membrane	Cell signaling	[21]
	HT-29 cells	Plasma membrane	Cell signaling	[21]
	Caco-2 cells	Plasma membrane	Wound healing	[86]
	NHEK	Plasma membrane	Cell signaling	[16]
	MDA-MB-231 & DU4475	Plasma membrane	Cancer cell migration & cell signaling	[15]
	HaCaT cells	Plasma membrane	Wound healing	[87]
	T-cells	Plasma membrane	Cell migration	[75]
AQP5	BxPC-3 cells	Plasma membrane	Cancer cell migration	[88]
AQP8	HeLa cells	Plasma & ER membranes	Cell signaling	[73]
	HepG2 cells	Inner mitochondrial membrane	Mitochondrial depolarization	[74]
AQP9	HepG2 cells	Plasma membrane	H_2O_2 induced cytotoxicity	[77]

NHEK: Neonatal human keratinocytes; BxPC-3 cells: Biopsy xenograft of Pancreatic Carcinoma line-3; MDA-MB-231 & DU4475: breast cancer cell line; ER: endoplasmic reticulum.

5. Involvement of aquaporin activity in dietary-derived redox change

5.1. Paradoxical antioxidant effect of dietary phenolics that generate H_2O_2

There are two perspectives on the mechanism underlying the antioxidant capacity of polyphenols. For direct antioxidant mechanism, polyphenols act in a non-oxidized state to effectively function as scavengers of ROS. In this scenario, the redox-active phenolic components engage in the scavenging of ROS through the transfer of either an electron or a hydrogen atom to the ROS molecule. Alternatively, polyphenols undergo oxidation beforehand, which enhances potential antioxidant effects. For instance, the oxidation of redox-active components facilitates a role that represents an indirect antioxidant mechanism. In this case, the antioxidant function is not triggered by the phenolic compound itself but rather by a metabolite that arises from its oxidation [102,106]. Polyphenols, upon oxidation into quinone forms, have the capability to engage in Michael addition reactions with cysteine residues found on Keap1 [27,28]. Additionally, extracellular polyphenols undergoing oxidation to produce H_2O_2 also play a substantial role in the activation of Nrf2 [31,107,89]. This represents a pivotal mechanism through which polyphenols contribute to cellular defense against oxidative stress (Fig. 4 (A)). Fig. 4(B) shows a schematic diagram that illustrates possible mechanisms for the autoxidation of polyphenols. Briefly, the transfer of electrons from the polyphenol (PhH) to an oxygen molecule results in the formation of an intermediate known as the *ortho*-semiquinone anion radical (Ph·). This intermediate then undergoes a radical-radical reaction, ultimately leading to the formation of o-quinone. Additionally, the *ortho*-semiquinone anion radical reacts with oxygen, giving rise to the generation of a superoxide anion radical ($O2^{\cdot-}$), thereby initiating a redox cycle [108]. When this O^{2-} is subsequently eliminated by the parent polyphenol, it leads to the production of o-quinone radicals and H_2O_2 [89,109]. Relative differences between autoxidation of phenolic acids have been ascribed to the specific structure and electronic configuration of the hydroxyl oxygen bound to the benzene ring molecule [89,90]. The presence of adjacent phenolic –OH groups is required for H_2O_2 generation, presumably due to the susceptibility of catechol structures to oxidation [110]. Former studies have demonstrated that high H_2O_2 concentrations are produced from polyphenol-rich beverages, such as cocoa, green tea, black tea and coffee during processing (See Table 4) [111]. Tea leaves, when chewed, produce H_2O_2 in saliva that corresponded to the polyphenol content [112]. Tea catechins, when present in certain types of cell-culture media, or buffer solutions also result in significant H_2O_2 production (See **Table 4**) [109,113–115]. The relative capacity of simpler phenolic acids to generate H_2O_2 in specific culture media devoid of pyruvate was also linked to subsequent intracellular concentrations in differentiated

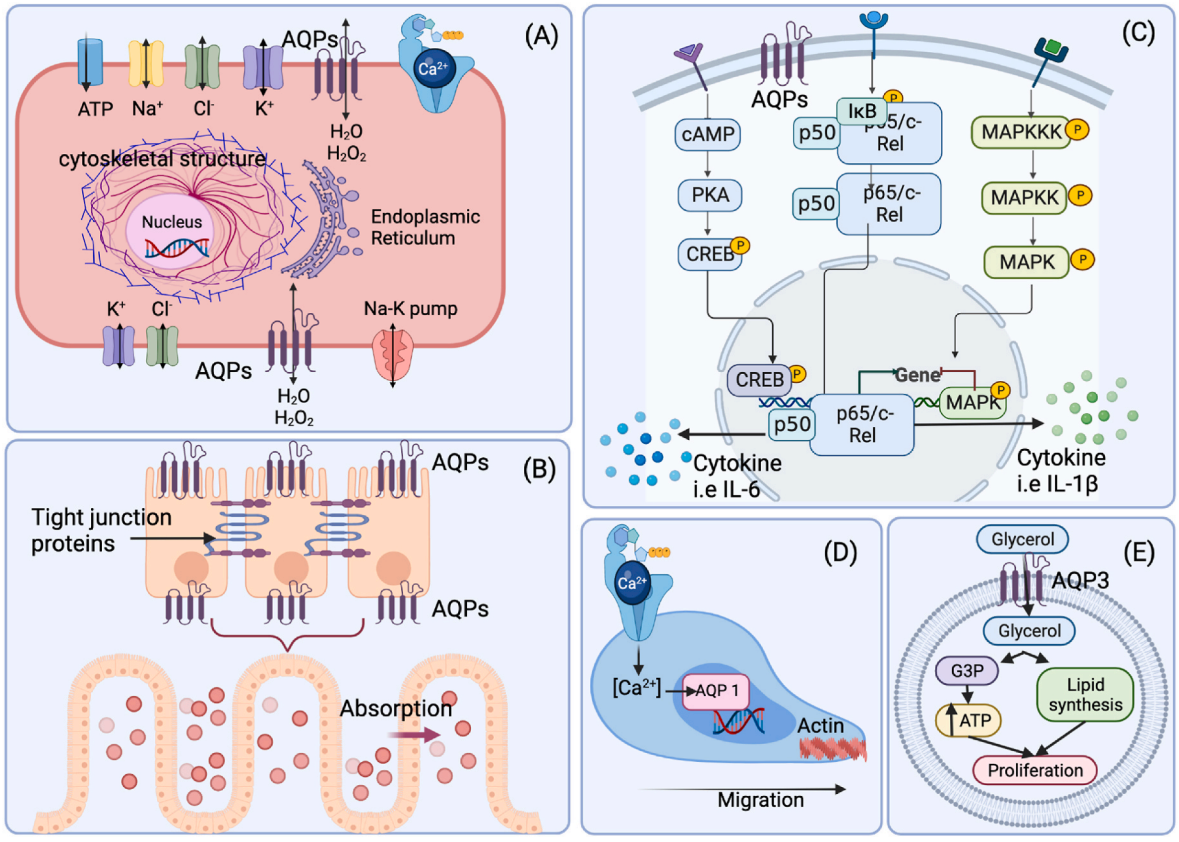

Fig. 3. A scheme showing the functionality of aquaporins. (A) Aquaporins involved in cytoskeletal structure by altering cell volume caused by abnormal Na^+/K^+flux. (B) Alteration of expression of intestinal AQPs produces changes in cell membrane fluidity, that affect drug and nutrient permeability and absorption. AQP3 for example influences intestinal barrier integrity that is linked to lower expression of enterocyte tight junctions. (C) Aquaporins involved in cascade of cell signaling and subsequent immune response. (D) Aquaporins involved in epithelial cell migration. (E) Aquaporins involved in cell proliferation caused by AQP3 facilitated glycerol entrance, which regulates the concentration of glycerol and adenosine triphosphate biosynthesis.

Caco-2 cells [90]. As mentioned, this effect was muted when catalase was added [17] and supports the findings of others that polyphenol induction of intracellular responses including mutagenicity and cell apoptosis are eliminated *in vitro* when catalase is added to the reaction mixture [116–118]. Another example of dietary involvement has to do with Maillard Reaction Products (MRPs), which have the capacity to induce NF-κB translocation in macrophages; a response attributed to the generation of H_2O_2 from coffee [93]. Finally, experiments using healthy volunteers having dietary intake of phenolic acids typical of many coffee drinking routines, showed increased urinary H_2O_2 output and an association between coffee consumption and reduced oxidative stress [111].

5.2. The link between dietary polyphenol intake and aquaporin expression

Evidence supporting the important interaction between bioactive phytochemicals and AQPs comes from studies with specific fruit drinks that relieved constipation in mice [122] and from Chinese medicines that are typically used to treat digestive disorders [123]. More specifically, genistein, a predominant isoflavone derived from soya-products, as well as other vegetables (e.g., broccoli and cauliflower) and seeds (sunflower and caraway), can increase expression of AQP1 and AQP4, respectively, and restore fluid absorption in the treatment of diarrhea [54]. Naringin, (flavanone-7-*O*-glcycoside) also increases the expression of AQP3 in both apical and lateral colon mucosal epithelial cells, together with enhanced messenger ribonucleic acid (mRNA) and protein [124] levels. Quercetin, another flavonoid, modulates intestinal water transport where the prevention of the loss of mucosa water permeability is associated with the induced expression of AQP3 and AQP8 at both mRNA and protein levels [125]. In contrast, food components that have laxative properties will typically lower the expression of AQP3, facilitating the absorption of water reaching the large intestine [126]. It is noteworthy that different polyphenolic compounds which regulate aquaporin expression, also parallel multiple examples of antioxidant mechanisms that involve multiple cell-signaling pathways. These include upregulation of cyclic adenosine monophosphate (cAMP)/Protein kinase A (PKA)/cAMP-responsive element binding protein (CREB) signal transduction pathway, NF-κB pathway and mitogen-activated protein kinase (MAPK) signaling pathway [54,127,128].

As previously mentioned, a connection between antioxidant/prooxidant activity of plant phenols with AQP function involves the generation of extracellular H_2O_2 and parallels increased intracellular H_2O_2 [90] and the regulation of intestinal oxidative stress [89,125,129,130]. Thus, different food systems composed of unique mixtures of specific phenolic acids are likely to have dual antioxidant/prooxidant functions that affect oxidative status by generating H_2O_2 production at ideal extracellular levels required to optimally interact with AQP receptors and regulate optimal intracellular uptake.

6. Conclusions

The expression “a healthy gut translates to a healthy life” can be supported by evidence that the intestine has a major role in establishing optimal whole body oxidative status through the involvement of dietary polyphenols that affect AQP expression and the intracellular uptake of H_2O_2. Thus, autoxidation reactions that occur with selective polyphenols with a predisposition to generate H_2O_2 is a required step in order to control the passive uptake of this messenger molecule by upregulating AQP expression. The result translates to a H_2O_2-triggered

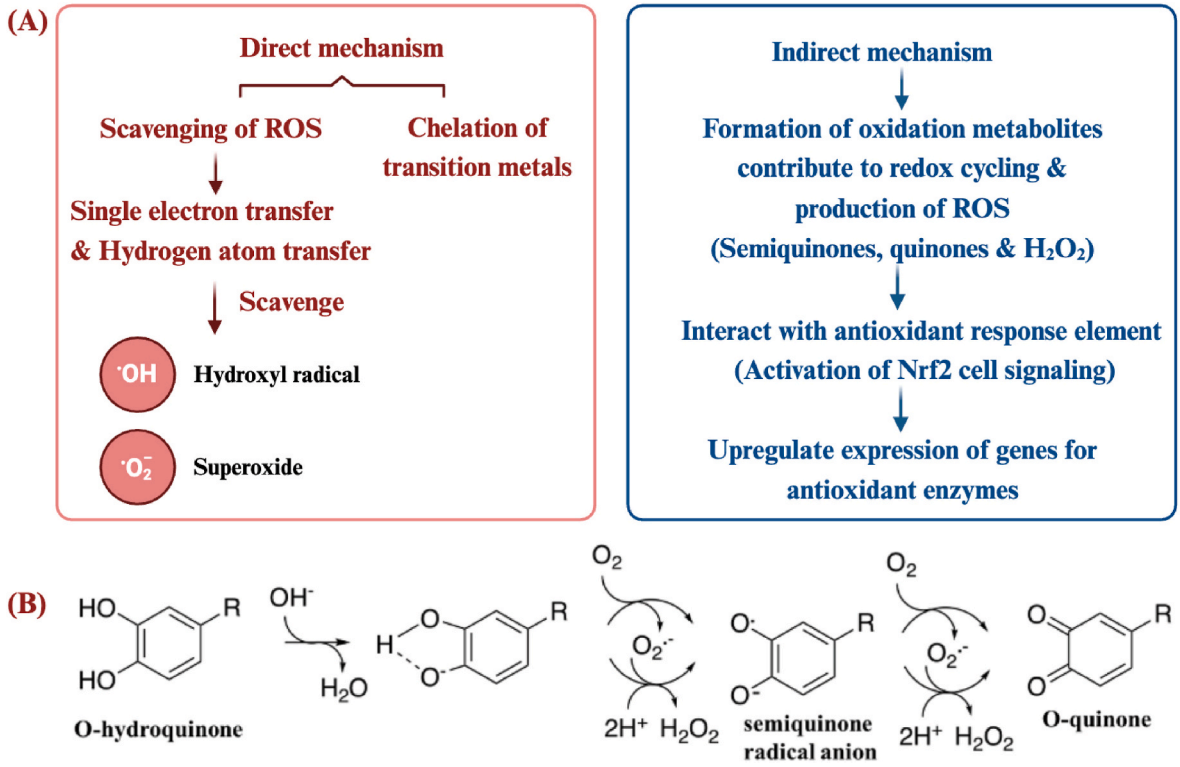

Fig. 4. (A). Direct and indirect antioxidant mechanisms of polyphenol. In the direct mechanism, polyphenols remain in a non-oxidized state and directly engage with ROS, effectively scavenging them by transferring electrons or hydrogen atoms to the ROS molecules. The indirect mechanism involves the prior oxidation of polyphenols, which enhances their antioxidant effects. These oxidized polyphenols activate antioxidant response element, such as Keap1-Nrf2 cell signaling, regulating gene expression and resulting in the upregulation of antioxidant enzymes [102,106]. Fig. 4 (B). A schematic diagram that shows possible mechanisms for the autoxidation of polyphenols. Reproduced from Refs. [119–121].

Table 4
Examples of H_2O_2 generated by oxidation of polyphenol in culture medium (Adapted from Refs. [89,90,91] with modifications).

Polyphenol	Description	Reference
Catechols	H_2O_2 generation in extracellular space results in cytotoxicity	[92]
Caffeic acid	H_2O_2 generation in extracellular space results in intracellular H_2O_2 increase	[90]
Coffee polyphenols	Coffee produces high level of H_2O_2	[93,94]
Cyanidin-3-rutoside	H_2O_2 generation was involved to this observation	[95]
Epigallocatechin gallate	H_2O_2 generation contributed to cytotoxicity	[96]
Epigallocatechin gallate	Suppression via H2O2 was prevented by PEG-catalase	[97]
Gallic acid	H_2O_2 generation in extracellular space results in intracellular H_2O_2 increase	[90]
Grape seed	H_2O_2 generation was due to oxidation of phenolics in the medium	[98]
Green tea polyphenol	H_2O_2 generation contributed to this observation	[99]
Green tea & red wine polyphenol	Oxidation of green tea in cell culture media generate sufficient levels of H_2O_2	[100]
Quercetin, catechin	H_2O_2 generation in culture medium was involved	[101]
Resveratrol	H_2O_2 generation in culture medium contributed to cell signaling activation	[102]

intracellular down-stream signaling mechanism that protects against excessive ROS generation and onset of oxidative stress. In addition to the many studies that have shown AQP expression to be affected by various factors, future studies are needed to focus on defining how food choices that influence dietary intake levels of different plant polyphenols also modify intestinal aquaporin expression. We look forward to having food chemists/nutritionists and biochemists evaluate the antioxidant effectiveness of different bioactive polyphenols from different dietary sources using prooxidation capacity to define the optimal limits of H_2O_2 production needed to interact with AQPs and to ensure intestinal intracellular oxidative homeostasis through H_2O_2 targeted cell signaling.

Credit authorship contribution statement

KM: Conceptualization; Visualization; Writing-Original draft; Reviewing. D. D. Kitts: Funding acquisition, Conceptualization; Writing-Original draft; Reviewing and Editing.

Declaration of generative AI and AI-assisted technologies in writing process

The authors did not use, or rely, on Generative AI or AI-assisted Technologies while preparing this manuscript.

Declaration of competing interest

There is no conflict of interest among authors.

Data availability

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

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