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Oral enzymatic detoxification system: Insights obtained from proteome analysis to understand its potential impact on aroma metabolization

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Abstract

The oral cavity is an entry path into the body, enabling the intake of nutrients but also leading to the ingestion of harmful substances. Thus, saliva and oral tissues contain enzyme systems that enable the early neutralization of xenobiotics as soon as they enter the body. Based on recently published oral proteomic data from several research groups, this review identifies and compiles the primary detoxification enzymes (also known as xenobiotic-metabolizing enzymes) present in saliva and the oral epithelium. The functions and the metabolic activity of these enzymes are presented. Then, the activity of these enzymes in saliva, which is an extracellular fluid, is discussed with regard to the salivary parameters. The next part of the review presents research evidencing oral metabolization of aroma compounds and the putative involved enzymes. The last part discusses the potential role of these enzymatic reactions on the perception of aroma compounds in light of recent pieces of evidence of in vivo oral metabolization of aroma compounds affecting their release in mouth and their perception. Thus, this review highlights different enzymes appearing as relevant to explain aroma metabolism in the oral cavity. It also points out that further works are needed to unravel the effect of the oral enzymatic detoxification system on the perception of food flavor in the context of the consumption of complex food matrices, while considering the impact of food oral processing. Thus, it constitutes a basis to explore these biochemical mechanisms and their impact on flavor perception.

KEYWORDS
aroma, detoxification enzymes, metabolism, oral cavity, saliva

1 | INTRODUCTION

The oral cavity is an entry path into the body that allows the ingestion of food, which is necessary for the intake of macro- and micronutrients. However, food intake also facilitates the entry of substances or biological entities that may be harmful. This possibility explains the presence of enzymatic defenses at the oral level, especially in saliva. Saliva consists of fluid secreted by the salivary glands and periodontal tissues (crevicular gingival fluid). Saliva is composed of water, salts, proteins, cell debris, and microorganisms. The protein concentration in saliva is approximately 0.2–2.0 mg/ml, and more than 3000 different proteins are present (Denny et al., 2008; Sivadasan et al., 2015). These proteins fulfill various roles, such as defense against microorganisms (immunoglobulins and peroxidases), oral digestion (amylases), lubrication of the oral cavity (mucins), neutralization of toxic molecules (proline-rich proteins and histatins), and the transport of flavor molecules (lipocalins). Numerous families of enzymes, such as esterases, carbohydrases, oxidoreductases, proteases, and transferring enzymes (Chauncey, 1961; Chauncey et al., 1954), are present in saliva. Some of these enzymes are secreted by the salivary glands, while others are derived from the lysis of desquamated epithelial cells. Some proteins can also be of bacterial origin, given the presence of microbiota in the mouth. Not all oral proteins are found free in saliva. Some proteins are also present in the oral mucosa, either in the cells of the oral epithelium or bound to the surface of the oral epithelium, forming the mucosal pellicle, a thin protein layer covering the oral mucosa (Canon et al., 2018).

Among salivary enzymes, some are detoxification enzymes (also known as xenobiotic-metabolizing enzymes, or XMEs), which metabolize exogenous or endogenous substances, thereby decreasing their reactivity and facilitating their excretion into the circulatory system (Liska, 1998). The presence of XMEs has been reported in the oral mucosa (Mallery et al., 2011), tongue (Takiguchi et al., 2010), and saliva (Alam et al., 2016; Fabrini et al., 2014). These studies have also demonstrated the ability of oral XMEs to metabolize pharmaceutical active ingredients or molecules present in food. In particular, detoxification systems have been suggested to be important for the early management of orally toxic xenobiotics (Yamahara & Lee, 1993). Notably, the consumption of certain foods, such as Brassicaceae vegetables, can increase the salivary concentration of specific XMEs (Sreerama et al., 1995). Very recently, it was also suggested that oral XMEs may be involved in the metabolism of aroma compounds in the mouth and therefore may modulate flavor perception (Ployon et al., 2020). Aroma compounds are low-molecular-weight odorant molecules released in the mouth during the eating process. These compounds can reach the olfactory mucosa via the retronasal route, where they activate olfactory receptors present in the plasma membranes of sensory neurons. Importantly, numerous aroma compounds are molecules that are toxic at high concentrations. For instance, aldehydes are highly reactive due to their functional group that enable them to undergo various reactions including covalent adducts with biomolecules (O'Brien et al., 2005). However, the low concentration at which they are present in foods (usually below the "no-adverse-effect-level" NOAEL concentration) generally precludes any harmful effects (Dinu et al., 2020), although their metabolization by XME is possible.

The phenomenon of the metabolization of aroma compounds in the mouth was first reported in the early 1980s (Hussein et al., 1983). The authors observed a decrease in aroma compounds concomitant with the appearance of the corresponding metabolites after rinsing the mouth with aroma solutions (Hussein et al., 1983). In 2002, Buettner confirmed that salivary compounds decrease the release of esters, aldehydes and thiols, suggesting that they play the role of salivary enzymes (Buettner, 2002a, 2002b). More recently, the metabolization of carbonyl compounds by saliva has been reported by Muñoz and coworkers (Muñoz-González et al., 2018; Muñoz-González et al., 2019) and was found to be stimulated by Nicotinamide adenine dinucleotide (NADH), which strongly supports the involvement of Nicotinamide adenine dinucleotide (phosphate) (NAD(P)H)-dependent oxidoreductases. In agreement with these findings, oxidoreduction of carbonyl compounds was also observed in the presence of an oral mucosa model (Ployon et al., 2020). Taken together, these studies suggest the involvement of XMEs in the metabolization of aroma molecules. This metabolization may affect both the quantity (decrease of the initial molecule) and the quality (formation of new molecules that may be odorant) of aroma compounds reaching the olfactory receptors. From a sensory perspective, it was proposed that metabolic activity in the nasal and oral cavities impacts odorant perception (Ijichi et al., 2019; Robert-Hazotte, Schoumacker, et al., 2019; Starkenmann et al., 2008). This hypothesis has been confirmed by two recent studies. The first study reported that metabolites impact the activation of olfactory receptors and perception (Ijichi et al., 2019), while the second demonstrated that aroma metabolization by saliva and the oral mucosa modulate the length of aroma persistence (Muñoz-Gonzalez et al., 2021).

The purpose of this review is to examine published proteomes to provide a broad and detailed inventory of XMEs present in saliva and the oral epithelium and to discuss their potential activities with aroma compounds. After introducing the detoxification steps, the identified enzymes and their activities are presented in the oral context. When data in the oral context were lacking, choice was made to discuss information about metabolization at

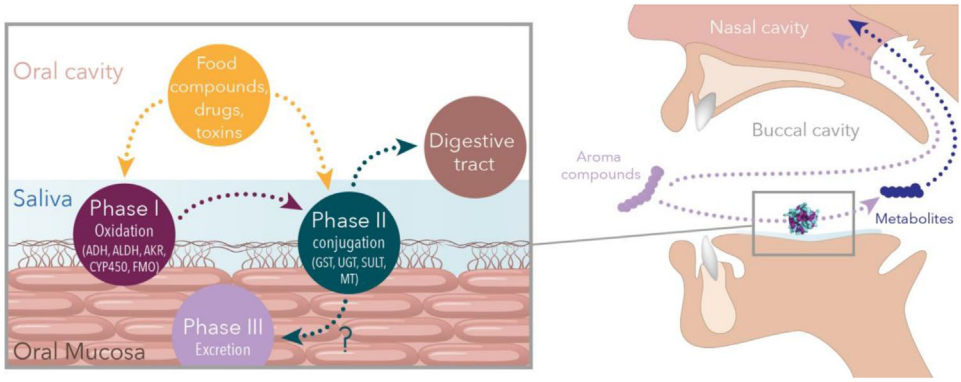

FIGURE 1 Enzymatic detoxification system in the oral cavity. Scheme summarizing the entry of xenobiotics in the oral cavity and their management by the detoxification system present in the saliva or in the oral mucosa

the olfactory level as the same enzyme families exist in the oral and nasal cavities (Uhlén et al., 2015) and some biochemical reactions involving these enzymes have been reported in both cavities (Ijichi et al., 2019). However, it is important to consider that the activity of these enzymes in the oral cavity may be modulated by different physiological parameters and the presence of food, which, for example, can affect the pH, and thus the enzymatic activities, despite the high buffering capacity of saliva. Finally, we review the metabolic activities toward aroma compounds found in saliva and the oral epithelium and discuss the potential candidate enzymes that may be involved in these various reactions.

2 | CHARACTERIZATION OF THE DETOXIFICATION SYSTEM IN THE ORAL CAVITY

2.1 | Generalities on oral detoxification

Xenobiotic detoxification has been historically classified into three groups of protein actors according to their level of action in the detoxification process (Figure 1): phase I enzymes activate xenobiotic compounds (usually by oxidation). This phase includes such enzymes as cytochromes P450 (CYP450) or flavin monooxygenases (FMOs; Liska, 1998). The functionalized compounds are subsequently conjugated to hydrophilic groups (or directly without phase I oxidation) by phase II enzymes, such as Uridine diphosphate (UDP)-glucuronosyl transferases (UGTs) or glutathione transferases (GSTs; Jancova et al., 2010). The products formed are conjugates whose solubility is generally higher than that of the corresponding substrates. Finally, phase III transport systems primarily act at the membrane level ("ATP-Binding Cassette" ABC transporters or "Multidrug Resistance Protein" MRP transporters) to facilitate the excretion of the formed conjugates from the cell to the circulatory system when they are generated in the cell. In the oral context, studies have reported the presence of phase I (Sreerama et al., 1995; Takiguchi et al., 2010; Yamahara & Lee, 1993) and phase II (Fabrini et al., 2014; Giebultowicz et al., 2009; Mallery et al., 2011) XMEs, whereas phase III excretion systems are poorly described at the oral level, as noted in a recent review (Bierbaumer et al., 2018). Phase III systems are probably only present at the level of the oral mucosa. Indeed, saliva is an extracellular biological fluid continuously secreted and renewed. Thus, at the opposite of the intracellular fluid in which metabolites can accumulate, they do not accumulate in saliva as they are diluted in the continuous secretion and eliminated with saliva swallowing.

2.2 | Exploration of oral proteomes

Based on recent proteomic data, we have established a list of the families of detoxification enzymes that are present in the oral cavity, with a focus being placed on those that may react with aroma compounds. To this end, we explored four salivary proteomes and one from the buccal epithelium (Denny et al., 2008; Ghosh et al., 2012; Grassl et al., 2016; Pappa et al., 2018; Sivadasan et al., 2015). For each proteome, all isoforms of the main families of phase I and II detoxification enzymes (Hodges & Minich, 2015; Liska, 1998) were screened by their names and listed. A focus was placed on the XMEs showing reactivity with odorant molecules, which is well documented in the context of nasal mucosa (Dahl & Hadley, 1991; Heydel et al., 2019; Sarkar, 1992). In addition, we also included metabolic enzymes that may have reactivity with aroma compounds (e.g., carbonic anhydrases [CAs] primarily catalyze CO_2 hydration but also have esterase activity with several compounds and thus belong to XMEs; Supuran, 2008). Ninety-one XMEs were identified among the five proteomes analyzed, which represents approximately 2% of the total salivary proteins (4876 proteins confidently detected at

the highest level in saliva by Pappa et al., 2018). These XMEs belong to three groups following the official enzyme nomenclature (Figure 2): NAD(P)H-dependent oxidoreductases (Table 1), transferases (Table 2), and hydrolases (Table 3). The greatest diversity of salivary XMEs is found in the group of oxidoreductases (48 enzymes from 8 families) with several isoforms of major families, such as CYP450, aldehyde dehydrogenase (ALDH) and short-chain dehydrogenase/reductase (SDR; Figure 2). Concerning transferases, five families, among which the two main UGT and GST families, were identified. The group of oral hydrolases includes four families: CA, carboxyl esterase (CES), epoxide hydrolase (EPHX), and paraoxonase (PON)/arylesterase. In the following section, the functions of each enzyme are indicated, with a focus being placed on those relevant in the oral context when they are known.

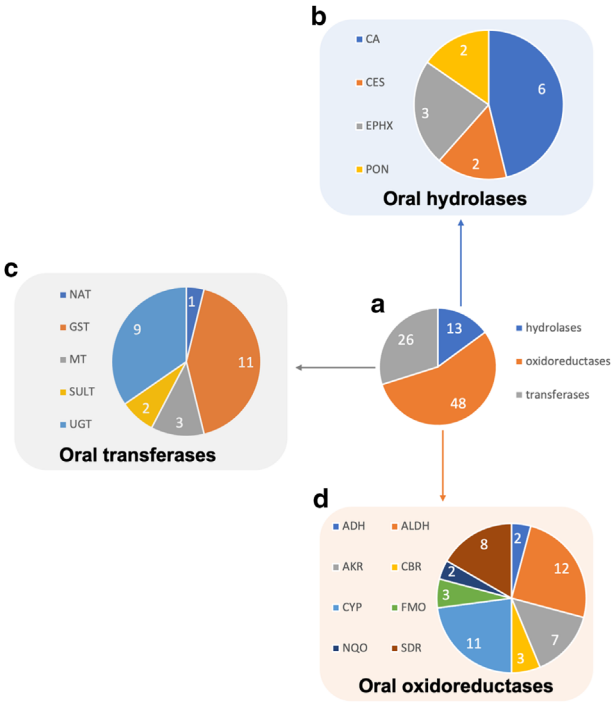

FIGURE 2 Repartition of oral XMEs identified from proteomic data. (a) Repartition of XMEs between three groups: oxidoreductases, transferases, and hydrolases. Number of members for each enzyme family is given. (b) Enzyme families identified in the hydrolases group. (c) Enzyme families identified in the transferases group. (d) Enzyme families identified in the oxidoreductases group
Abbreviations: ADH, alcohol dehydrogenase; AKR, aldo-ketoreductase; ALDH, aldehyde dehydrogenase; CA, carbonic anhydrase; CBR, carbonyl reductase; CES, carboxyl esterase; CYP, cytochrome P450; EPHX, epoxide hydrolase; FMO, flavin-monooxygenase; GST, glutathione transferase; MT, methyl transferase; NAT, *N*-acetyl transferase; NQO, NADPH-quinone oxidoreductase; PON, paraoxonases; SDR, short-chain dehydrogenases/reductase; SULT, sulfotransferase; UGT, UDP-glucuronosyl transferase.

3 | XMEs IDENTIFIED FROM SALIVARY AND ORAL MUCOSA PROTEOMES

3.1 | Oxidoreductases

Oxidoreductases constitute a large family of enzymes that use NAD(P)H to catalyze oxidation or reduction reactions of chemicals (Selles Vidal et al., 2018). Various chemical families can be metabolized by oxidoreductases, such as amines, sulfur compounds, alcohols, ketones, carboxylic acids, and aldehydes (Table 1). Based on the proteomes analyzed, we identified eight families of enzymes present in saliva and able to catalyze such reactions, namely, alcohol dehydrogenases (ADHs), ALDHs, aldo-ketoreductases (AKRs), carbonyl reductases (CBRs), CYPs, FMOs, NADPH quinone oxidoreductases (NQOs), and SDRs (Table 1). Some isoforms of the families ADH, ALDH, AKR, CBR, CYP450, and SDR were also found in the oral mucosa (Table 1, asterisks). Some families are known to catalyze both oxidation and reduction (i.e., forward and reverse reactions) depending on the availability of reduced or oxidized cofactors and on the substrate (e.g., ADH, ALDH, AKR, NQO), while other enzymes are mainly specific for either oxidation (e.g., CYP450, FMO) or reduction (CBR, SDR; Selles Vidal et al., 2018).

3.1.1 | Aldehyde dehydrogenase

Aldehydes form an important family of aroma compounds known for their reactivity in the mouth (Buettner, 2002b; Muñoz-González et al., 2018; Ployon, et al., 2020). The concentration of aldehydes in food is low. Their toxicity is not a concern with regard to their concentration in food (e.g., for benzaldehyde, NOAEL of 400 mg/kg in rats oral studies, while concentration in food is 0.0003 to 8.9 ppm (Final Report on the Safety Assessment of Benzaldehyde, 2006), therefore they do not present a risk for human health. Nevertheless, they can be metabolized upon entrance in the oral cavity. Aldehydes can be oxidized to carboxylic acid by ALDH enzymes. The main salivary ALDH is the isoform ALDH3A1, which exhibits specific expression in saliva (Giebultowicz et al., 2009). ALDH3A1 is overexpressed after consumption of broccoli and coffee (Sreerama et al., 1995). Salivary ALDH3A1 participates in the detoxification of exogenous aldehydes entering the oral cavity, and its activity is modulated by compounds present in food or water. It is activated by thymoquinone (Laskar et al., 2017) and sulforaphane (Alam et al., 2016) but

TABLE 1 Oxidoreductases identified from oral proteomes and representative substrates from the literature

Family	Enzyme	Gene	Accession number	Metabolizing functions	Cofactor or cosubstrate	Representative substrates	References	Proteome references
Alcohol dehydrogenase (ADH)	Alcohol dehydrogenase class-3*$	ADH5	P11766	Oxidoreduction	NAD(P)H	Long-chain alcohols and fatty acids, hydroxymethyl-glutathione	(Engeland et al., 1993)	Ghosh et al. (2012), Grassl et al. (2016), Pappa et al. (2018), Sivadasan et al. (2015)
	Alcohol dehydrogenase class-4	ADH7	P40394	Oxidoreduction	NAD(P)H	Alcohols, aldehydes, and fatty acids	(Allali-Hassani et al., 1998)	(Grassl et al., 2016; Pappa et al., 2018; Sivadasan et al., 2015)
Aldehyde dehydrogenase (ALDH)	Aldehyde dehydrogenase 1 isoform A1	ALDH1A1	P00352	Oxidoreduction	NAD(P)H	Long-chain aldehydes	(Xiao et al., 2009)	(Grassl et al., 2016; Pappa et al., 2018; Sivadasan et al., 2015)
	Aldehyde dehydrogenase 1 isoform A2	ALDH1A2	O94788	Oxidoreduction	NAD(P)H	Long-chain aldehydes	(Y. Chen et al., 2018)	(Grassl et al., 2016; Sivadasan et al., 2015)
	Aldehyde dehydrogenase 1 isoform A3	ALDH1A3	P47895	Oxidoreduction	NAD(P)H	Trans-retinal	(Moretti et al., 2016)	(Grassl et al., 2016; Pappa et al., 2018; Sivadasan et al., 2015)
	Aldehyde dehydrogenase 1 isoform B1	ALDH1B1	P30837	Oxidoreduction	NAD(P)H	Aliphatic aldehydes	(Y. Chen et al., 2018)	(Ghosh et al., 2012)
	Aldehyde dehydrogenase 2, mitochondrial*$	ALDH2	P05091	Oxidoreduction	NAD(P)H	Acetaldehyde, 4HNE, MDA	(Y. Chen et al., 2018)	(Ghosh et al., 2012; Grassl et al., 2016; Pappa et al., 2018; Sivadasan et al., 2015)
	Aldehyde dehydrogenase 3 isoform A1$	ALDH3A1	P30838	Oxidoreduction	NAD(P)H	Medium-, long-chain, and aromatic aldehydes	(Hsu et al., 1992)	(Denny et al., 2008; Sivadasan et al., 2015) (Grassl et al., 2016; Pappa et al., 2018)
	Aldehyde dehydrogenase 3 isoform A2*	ALDH3A2	P51648	Oxidoreduction	NAD(P)H	Medium- and long-chain aldehydes	(Kelson et al., 1997)	(Ghosh et al., 2012; Grassl et al., 2016; Pappa et al., 2018)
	Aldehyde dehydrogenase 3 isoform B1	ALDH3B1	P43353	Oxidoreduction	NAD(P)H	Medium-, long-chain and aromatic aldehydes	(Marchitti et al., 2007)	(Grassl et al., 2016)
	Aldehyde dehydrogenase 4 isoform A1*$	ALDH4A1	P30038	Oxidoreduction	NAD(P)H	L-Glutamate 5-semialdehyde	(Srivastava et al., 2012)	(Denny et al., 2008; Ghosh et al., 2012; Grassl et al., 2016; Pappa et al., 2018)
	Aldehyde dehydrogenase 7 isoform A1	ALDH7A1	P49419	Oxidoreduction	NAD(P)H	Long-chain aldehydes	(Brocker et al., 2010)	(Pappa et al., 2018)

(Continues)

TABLE 1 (Continued)

Family	Enzyme	Gene	Accession number	Metabolizing functions	Cofactor or cosubstrate	Representative substrates	References	Proteome references
	Aldehyde dehydrogenase 9 isoform A1$	ALDH9A1	P49189	Oxidoreduction	NAD(P)H	4-(Trimethyl)aminobuta	(Kikonyogo & Pietruszko, 1996)	(Denny et al., 2008; Grassl et al., 2016; Pappa et al., 2018; Sivadasan et al., 2015)
	Aldehyde dehydrogenase 16 isoform A1	ALDH16A	Q8IZ83	Oxidoreduction	NAD(P)H	ND	ND	(Ghosh et al., 2012)
Aldo-keto reductase (AKR)	Aldo-keto reductase 1 isoform A1*$	AKR1A1	P14550	Oxidoreduction	NAD(P)H	Aromatic and aliphatic aldehydes, ketones, and acids	(O'Connor et al., 1999)	(Ghosh et al., 2012; Grassl et al., 2016; Pappa et al., 2018; Sivadasan et al., 2015)
	Aldo-keto reductase 1 isoform B1*$	AKR1B1	P15121	Oxidoreduction	NAD(P)H	Dietary aldehydes, ketones, and glutathione conjugates	(Shen et al., 2011)	(Ghosh et al., 2012; Grassl et al., 2016; Pappa et al., 2018; Sivadasan et al., 2015)
	Aldo-keto reductase 1 isoform B10	AKR1B10	O60218	Oxidoreduction	NAD(P)H	Dietary aldehydes, ketones, and glutathione conjugates	(Shen et al., 2011)	(Grassl et al., 2016; Pappa et al., 2018; Sivadasan et al., 2015)
	Aldo-keto reductase 1 isoform C1	AKR1C1	Q04828	Oxidoreduction	NAD(P)H	Hydroxysteroids	(Zhang et al., 2000)	(Pappa et al., 2018)
	Aldo-keto reductase 1 isoform C2	AKR1C2	P52895	Oxidoreduction	NAD(P)H	Hydroxysteroids	(Hara et al., 1996)	(Grassl et al., 2016; Pappa et al., 2018)
	Aldo-keto reductase 1 isoform C3*	AKR1C3	P42330	Oxidoreduction	NAD(P)H	Hydroxysteroids	(Khanna et al., 1995)	(Ghosh et al., 2012),(Grassl et al., 2016; Pappa et al., 2018)
	Aldo-keto reductase 7 isoform A2*$	AKR7A2	O43488	Oxidoreduction	NAD(P)H	Aromatic aldehydes	(Ireland et al., 1998)	(Ghosh et al., 2012; Sivadasan et al., 2015) (Grassl et al., 2016; Pappa et al., 2018)
Carbonyl reductase (CBR)	Carbonyl reductase 1*$	CBR1	P16152	Reduction	NAD(P)H	Aldehydes, ketones, glutathione conjugates	(Bateman et al., 2008)	(Ghosh et al., 2012; Sivadasan et al., 2015) (Grassl et al., 2016; Pappa et al., 2018)
	Carbonyl reductase 3	CBR3	O75828	Reduction	NAD(P)H	Aldehydes, ketones	(Miura et al., 2008)	(Grassl et al., 2016; Pappa et al., 2018)
	Carbonyl reductase 4	CBR4	Q8N4T8	Reduction	NAD(P)H	Quinones	(Endo et al., 2008)	(Grassl et al., 2016)

(Continues)

TABLE 1 (Continued)

Family	Enzyme	Gene	Accession number	Metabolizing functions	Cofactor or cosubstrate	Representative substrates	References	Proteome references
Cytochrome P450 (CYP)	Cytochrome P450 1A1	CYP1A1	P04798	Oxidation	Heme, NAD(P)	Fatty acids, aromatic amines, PAHs	(Mescher & Haarmann-Stemmann, 2018)	(Pappa et al., 2018)
	Cytochrome P450 2E1	CYP2E1	P05181	Oxidation	Heme, NAD(P)	Fatty acids, alcohols, aromatic amines, PAHs	(Chen et al., 2019)	(Grassl et al., 2016)
	Cytochrome P450 2J2	CYP2J2	P51589	Oxidation	Heme, NAD(P)	Fatty acids, various drugs	(Solanki et al., 2018)	(Grassl et al., 2016)
	Cytochrome P450 2S1*	CYP2S1	Q96SQ9	Oxidation	Heme, NAD(P)	PAHs, retinoids, eicosanoids	(Saarikoski et al., 2005)	(Ghosh et al., 2012; Grassl et al., 2016)
	Cytochrome P450 4F2	CYP4F2	P78329	Oxidation	Heme, NAD(P)	Fatty acids, eicosanoids, vitamins E and K	(Alvarellos et al., 2015)	(Grassl et al., 2016; Pappa et al., 2018)
	Cytochrome P450 4F3	CYP4F3	Q08477	Oxidation	Heme, NAD(P)	Fatty acids, aromatic amines	(Corcos et al., 2012)	(Grassl et al., 2016)
	Cytochrome P450 4F11	CYP4F11	Q9HBI6	Oxidation	Heme, NAD(P)	Fatty acids, vitamin K	(Guengerich et al., 2016)	(Grassl et al., 2016)
	Cytochrome P450 4F12	CYP4F12	Q9HCS2	Oxidation	Heme, NAD(P)	Fatty acids	(Guengerich et al., 2016)	(Grassl et al., 2016)
	Cytochrome P450 4F22	CYP4F22	Q6NT55	Oxidation	Heme, NAD(P)	Fatty acids	(Ohno et al., 2015)	(Grassl et al., 2016; Pappa et al., 2018)
	Cytochrome P450 20A1	CYP20A1	Q6UW02	Oxidation	Heme, NAD(P)	ND	(Guengerich et al., 2016)	(Grassl et al., 2016)
	Cytochrome P450 51A1	CYP51A1	Q16850	Oxidation, demethylation	Heme, NAD(P)	Sterols	(Guengerich et al., 2016)	(Grassl et al., 2016; Pappa et al., 2018)
Flavin-containing monooxygenase (FMO)	Flavin-containing monooxygenase 1	FMO1	Q01740	Oxidation	NAD(P)	Amines, sulfur compounds	(Krueger & Williams, 2005)	(Grassl et al., 2016)
	Flavin-containing monooxygenase 2	FMO2	Q99518	Oxidation	NAD(P)	Amines, sulfur compounds	(Krueger & Williams, 2005)	(Grassl et al., 2016; Pappa et al., 2018)

(Continues)

TABLE 1 (Continued)

Family	Enzyme	Gene	Accession number	Metabolizing functions	Cofactor or cosubstrate	Representative substrates	References	Proteome references
	Flavin-containing monooxygenase 4	FMO4	P31512	Oxidation	NAD(P)	Amines, sulfur compounds	(Krueger & Williams, 2005)	(Pappa et al., 2018)
NADPH quinone oxidoreductase (NQO)	NADPH-quinone oxidoreductase 1 (DT-diaphorase)	NQO1	P15559	Oxidoreduction	NAD(P)H, FAD	Quinones	(Bianchet et al., 2004)	(Grassl et al., 2016; Pappa et al., 2018)
	NADPH-quinone oxidoreductase 2	NQO2	P16083	Oxidoreduction	*N*-ribosyl nicotinamide, FAD	Quinones	(Calamini et al., 2008)	(Grassl et al., 2016; Sivadasan et al., 2015)
Short-chain dehydrogenase/reductase (SDR)	Dehydrogenase/reductase SDR 1	DHRS1	Q96LJ7	Reduction	NAD(P)H	Steroids	(Zemanova et al., 2019)	(Grassl et al., 2016; Pappa et al., 2018)
	Dehydrogenase/reductase SDR 3	DHRS3	O75911	Reduction	NAD(P)H	Trans-retinal	(Haeseleer et al., 1998)	(Grassl et al., 2016)
	Dehydrogenase/reductase SDR 4*	DHRS4	Q9BTZ2	Reduction	NAD(P)H	Steroids, carbonyl compounds	(Endo et al., 2008)	(Ghosh et al., 2012) (Grassl et al., 2016; Pappa et al., 2018)
	Dehydrogenase/reductase SDR 7	DHRS7	Q9Y394	Reduction	NAD(P)H	Steroids, aromatic ketones	(Zemanova et al., 2017)	(Grassl et al., 2016; Pappa et al., 2018)
	Dehydrogenase/reductase SDR 7B	DHRS7B	Q6IAN0	ND	ND	ND	ND	(Grassl et al., 2016; Pappa et al., 2018)
	Dehydrogenase/reductase SDR 9	DHRS9	Q9BPW9	Reduction	NAD(P)H	Steroids	(Chetyrkin et al., 2001)	(Grassl et al., 2016; Pappa et al., 2018)
	Dehydrogenase/reductase SDR 11	DHRS11	Q6UWP2	Reduction	NAD(P)H	Steroids, aldehydes, and ketones	(Endo et al., 2016)	(Grassl et al., 2016; Pappa et al., 2018)
	Dicarbonyl xylulose reductase (DCXR)	DCXR	Q7Z4W1	Reduction	NAD(P)H	Carbonyl compounds, sugars	(Zaccone et al., 2015)	(Grassl et al., 2016; Pappa et al., 2018)

Note: Gene names and Uniprot accession numbers are given for each isoform. Representative substrates reported in biochemical studies are indicated with the corresponding references. Proteins found in oral epithelium are marked with the symbol *. Proteins identified in at least four of the five proteomes analyzed are marked with the symbol $.
Abbreviation: ND, not determined.

TABLE 2 Transferases identified from oral proteomes and representative substrates from the literature

Family	Enzyme	Gene	Accession number	Metabolizing functions	Cofactor or cosubstrate	Representative substrates	References	Proteome references
Arylamine *N*-acetyl transferase (NAT)	Arylamine *N*-acetyl transferase 1	NAT1	P18440	*N*- and *O*-Acetyl transfer	Acetyl-CoA	Arylamines and heterocyclic amines	(Sim et al., 2014)	(Grassl et al., 2016)
Glutathione transferase (GST)	Glutathione transferase Alpha isoform 1	GSTA1	P08263	GSH transfer	GSH	Halogenated compounds, ITCs, PAHs, epoxides, aldehydes, ketones, steroids	Hayes et al. (2005b), Kolm et al. (1995)	(Grassl et al., 2016; Pappa et al., 2018)
	Glutathione transferase Alpha isoform 4	GSTA4	O15217	GSH transfer	GSH	Halogenated compounds, aldehydes, ketones	(Hayes et al., 2005b)	(Grassl et al., 2016; Pappa et al., 2018)
	Glutathione transferase Kappa isoform 1*$	GSTK1	Q9Y2Q3	GSH transfer	GSH	Halogenated compounds, peroxides	(Hayes et al., 2005b)	(Ghosh et al., 2012; Sivadasan, 2015; Grassl et al., 2016; Pappa et al., 2018)
	Glutathione transferase Mu isoform 1	GSTM1	P09488	GSH transfer	GSH	Halogenated compounds, PAHs, epoxides, ketones	(Hayes et al., 2005b)	(Pappa et al., 2018; Sivadasan et al., 2015)
	Glutathione transferase Mu isoform 2	GSTM2	P28161	GSH transfer	GSH	Halogenated compounds, ketones, prostaglandins	(Hayes et al., 2005b)	(Pappa et al., 2018; Sivadasan et al., 2015)
	Glutathione transferase Mu isoform 3	GSTM3	P21266	GSH transfer	GSH	Halogenated compounds, prostaglandins	(Hayes et al., 2005b)	(Grassl et al., 2016; Pappa et al., 2018)
	Glutathione transferase Mu isoform 4	GSTM4	Q03013	GSH transfer	GSH	Halogenated compounds	(Hayes et al., 2005b)	(Pappa et al., 2018; Sivadasan et al., 2015)
	Glutathione transferase Omega isoform 1*$	GSTO1	P78417	Deglutathionylation, thiol transfer	GSH	Glutathionylated compounds and proteins, HED, GS-acetophenones, ascorbate	(Board & Menon, 2016)	(Denny et al., 2008; Ghosh et al., 2012) (Grassl et al., 2016; Pappa et al., 2018; Sivadasan et al., 2015)

(Continues)

TABLE 2 (Continued)

Family	Enzyme	Gene	Accession number	Metabolizing functions	Cofactor or cosubstrate	Representative substrates	References	Proteome references
	Glutathione transferase Pi isoform 1*$	GSTP1	P09211	GSH transfer	GSH	Halogenated compounds, ITCs, PAHs, aldehydes, ketones, peroxides	(Hayes et al., 2005b) (Kolm et al., 1995)	(Denny et al., 2008; Ghosh et al., 2012), (Grassl et al., 2016; Pappa et al., 2018; Sivadasan et al., 2015)
	Glutathione transferase Theta isoform 1	GSTT1	P30711	GSH transfer	GSH	Halogenated compounds, epoxides	(Hayes et al., 2005b)	(Grassl et al., 2016; Pappa et al., 2018)
	Glutathione transferase Theta isoform 2	GSTT2	P0CG29	GSH transfer	GSH	Peroxides, menaphtyl sulfate	(Hayes et al., 2005b)	(Grassl et al., 2016; Pappa et al., 2018)
Methyltransferase (MT)	Catechol *O*-methyl transferase*	COMT	P21964	Methyl transfer	SAM	Catechols, polyphenols	(Weinshilboum et al., 1999)	(Grassl et al., 2016; Pappa et al., 2018)
	Thiopurine *S*-methyltransferase	TPMT	P51580	Methyl transfer	SAM	Aromatic sulfur compounds	(Weinshilboum et al., 1999)	(Grassl et al., 2016; Pappa et al., 2018)
	Histamine *N*-methyl transferase	HNMT	P50135	Methyl transfer	SAM	Heterocyclic amines	(Weinshilboum et al., 1999)	(Grassl et al., 2016)
Sulfotransferase (SULT)	Sulfotransferase 1A1	SULT1A1	P50225	Sulfonate transfer	PAPS	Aromatic alcohols, steroids	(Gamage et al., 2006)	(Grassl et al., 2016; Sivadasan et al., 2015)
	Sulfotransferase 2B1	SULT2B1	O00204	Sulfonate transfer	PAPS	Steroids	(Gamage et al., 2006)	(Grassl et al., 2016; Pappa et al., 2018)

(Continues)

TABLE 2 (Continued)

Family	Enzyme	Gene	Accession number	Metabolizing functions	Cofactor or cosubstrate	Representative substrates	References	Proteome references
UDP-Glucuronosyl transferase (UGT)	UDP-glucuronosyl transferase 1-1*	UGT1A1	P22309	Glucuronosyl transfer	UDP-glucuronate	Bilirubin, polyphenols, steroids, hydroxypyrene	(Lv et al., 2019)	(Grassl et al., 2016; Pappa et al., 2018)
	UDP-glucuronosyl transferase 1–3*	UGT1A3	P35503	Glucuronosyl transfer	UDP-glucuronate	Bilirubin, polyphenols, steroids, tetrazole drugs	(Lv et al., 2019)	(Grassl et al., 2016)
	UDP-glucuronosyl transferase 1–4*	UGT1A4	P22310	Glucuronosyl transfer	UDP-glucuronate	Bilirubin, polyphenols, steroids	(Lv et al., 2019)	(Grassl et al., 2016; Pappa et al., 2018)
	UDP-glucuronosyl transferase 1–5*	UGT1A5	P35504	Glucuronosyl transfer	UDP-glucuronate	ND	(Lv et al., 2019)	(Grassl et al., 2016; Pappa et al., 2018)
	UDP-glucuronosyl transferase 1–6*	UGT1A6	P19224	Glucuronosyl transfer	UDP-glucuronate	Bilirubin, polyphenols, steroids, phenols	(Lv et al., 2019)	(Grassl et al., 2016; Pappa et al., 2018)
	UDP-glucuronosyl transferase 1–7*	UGT1A7	Q9HAW7	Glucuronosyl transfer	UDP-glucuronate	Bilirubin, steroids	(Lv et al., 2019)	(Grassl et al., 2016)
	UDP-glucuronosyl transferase 1–8*	UGT1A8	Q9HAW9	Glucuronosyl transfer	UDP-glucuronate	Bilirubin, steroids	(Lv et al., 2019)	(Grassl et al., 2016)
	UDP-glucuronosyl transferase 1–9*	UGT1A9	O60656	Glucuronosyl transfer	UDP-glucuronate	Bilirubin, steroids	(Lv et al., 2019)	(Grassl et al., 2016; Pappa et al., 2018)
	UDP-glucuronosyl transferase 1–10*	UGT1A10	Q9HAW8	Glucuronosyl transfer	UDP-glucuronate	Bilirubin, steroids	(Lv et al., 2019)	(Grassl et al., 2016)

Note: Gene names and Uniprot accession numbers are given for each isoform. Representative substrates reported in biochemical studies are indicated with the corresponding references. Proteins found in oral epithelium are marked with the symbol *. Proteins identified in at least four of the five proteomes analyzed are marked with the symbol $.
Abbreviation: ND, not determined.

TABLE 3 Hydrolases identified from oral proteomes and representative substrates from the literature

Family	Enzyme	Gene	Accession number	Metabolizing functions	Cofactor or cosubstrate	Representative substrates	References	Proteome references
Carbonic anhydrase (CA)	Carbonic anhydrase 1*$	CA1	P00915	Hydrolysis, hydration	H_2O	Aldehydes, esters, carboxylic and sulfonic acids	(Supuran, 2008)	(Ghosh et al., 2012; Grassl et al., 2016; Pappa et al., 2018; Sivadasan et al., 2015)
	Carbonic anhydrase 2*$	CA2	P00918	Hydrolysis, hydration	H_2O	Aldehydes, esters, carboxylic and sulfonic acids	(Supuran, 2008)	(Denny et al., 2008; Ghosh et al., 2012; Grassl et al., 2016; Pappa et al., 2018; Sivadasan et al., 2015)
	Carbonic anhydrase 3	CA3	P07451	Hydrolysis, hydration	H_2O	Aldehydes, esters, carboxylic and sulfonic acids	(Supuran, 2008)	(Denny et al., 2008)
	Carbonic anhydrase 4	CA4	P22748	Hydrolysis, hydration	H_2O	Aldehydes, esters, carboxylic and sulfonic acids	(Supuran, 2008)	(Grassl et al., 2016)
	Carbonic anhydrase 6*$	CA6	P23280	Hydrolysis, hydration	H_2O	Aldehydes, esters, carboxylic and sulfonic acids	(Supuran, 2008)	(Denny et al., 2008; Ghosh et al., 2012; Grassl et al., 2016; Pappa et al., 2018; Sivadasan et al., 2015)
	Carbonic anhydrase 13	CA13	Q8N1Q1	Hydrolysis, hydration	H_2O	Aldehydes, esters, carboxylic and sulfonic acids	(Supuran, 2008)	(Grassl et al., 2016)

(Continues)

TABLE 3 (Continued)

Family	Enzyme	Gene	Accession number	Metabolizing functions	Cofactor or cosubstrate	Representative substrates	References	Proteome references
Carboxyl esterase (CES)	Carboxyl esterase 1	CES1	P23141	Hydrolysis	H_2O	Esters	(Schindler et al., 1998)	(Grassl et al., 2016; Pappa et al., 2018; Sivadasan et al., 2015)
	Carboxyl esterase 2*$	CES2	O00748	Hydrolysis	H_2O	Esters, amides, lipids	(Pindel et al., 1997)	(Denny et al., 2008; Ghosh et al., 2012; Grassl et al., 2016; Pappa et al., 2018; Sivadasan et al., 2015)
Epoxide hydrolase (EPHX)	Epoxide hydrolase 1	EPHX1	P07099	Hydrolysis	H_2O	Epoxides	(Morisseau & Hammock, 2005)	(Grassl et al., 2016; Pappa et al., 2018)
	Epoxide hydrolase 2	EPHX2	H0YAW7	ND	ND	Epoxides	(Morisseau & Hammock, 2005)	(Grassl et al., 2016; Pappa et al., 2018)
	Epoxide hydrolase 3	EPHX3	Q9H6B9	Hydrolysis	H_2O	Epoxides	(Morisseau & Hammock, 2005)	(Grassl et al., 2016; Pappa et al., 2018)
Paraoxonase (PON)	Paraoxonase/arylesterase 1	PON1	P27169	Hydrolysis	H_2O	Lactones, aromatic esters, organophosphates	(Draganov et al., 2005)	(Grassl et al., 2016; Pappa et al., 2018; Sivadasan et al., 2015)
	Paraoxonase/arylesterase 2	PON2	Q15165	Hydrolysis	H_2O	Lactones, aromatic esters	(Draganov et al., 2005)	(Grassl et al., 2016; Pappa et al., 2018)

Note: Gene names and Uniprot accession numbers are given for each isoform. Representative substrates reported in biochemical studies are indicated with the corresponding references. Proteins found in oral epithelium are marked with the symbol *. Proteins identified in at least four of the five proteomes analyzed are marked with the symbol $.
Abbreviation: ND, not determined.

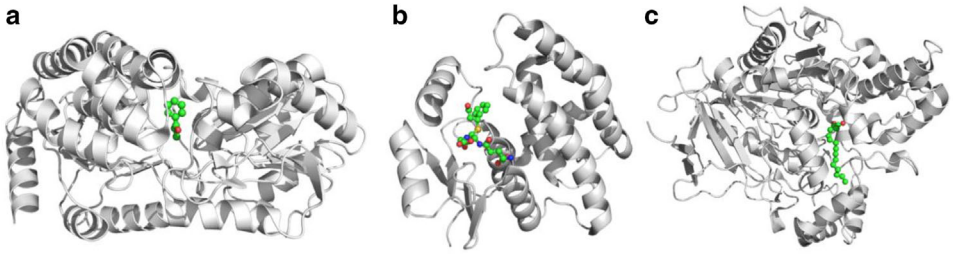

FIGURE 3 X-ray structures of oral XMEs bound to flavor compounds from the Protein Data Bank. For each enzyme, the X-ray structure is represented as white cartoon with the aroma molecule shown as sticks and spheres and colored green. (a) Aldehyde Dehydrogenase 3A1 bound to propiophenone derivative (PDB 3SZB; Khanna et al., 2011). (b) Glutathione Transferase Alpha 1 bound to glutathionyl-dihydrocinnamaldehyde (PDB 6YAW; Schwartz, Menetrier, et al., 2020). (c) Carboxyl Esterase 1 bound to palmitic acid (PDB 2DQY; Bencharit et al., 2006)

inhibited by arsenic (Younus et al., 2020). In a crystallographic study, the covalent binding of a propiophenone derivative (aroma compound with a fruity flavor) to a cysteine residue at the active site of ALDH3A1 (X-ray structure shown in Figure 3) was shown to inhibit its activity (Khanna et al., 2011). This finding suggests that the activity of ALDH3A1 could be modulated by a variety of aroma molecules and that biophysical and structural methods can be useful to characterize these processes. Although ALDH3A1 is probably the predominant ALDH in saliva, other isoforms are also present, notably four members of the ALDH1 group (Table 1). Importantly, ALDH1A1 was suggested to have a better capacity than ALDH3A1 to detoxify food aldehydes (e.g., up to 100-fold better catalytic efficacy with anisaldehyde, vanillin, or cinnamaldehyde; Solobodowska et al., 2012).

3.1.2 | Alcohol dehydrogenase, aldo-ketoreductase, carbonyl reductase, and short-chain dehydrogenase/reductase

Aldehydes can be oxidized or reduced by specific oxidoreductases depending on the NAD(P)H/NAD(P)$^+$ ratio. ADH, CBR, SDR, or AKR enzymes can reduce aldehydes into their corresponding alcohols (Barski et al., 2008; Selles Vidal et al., 2018). ADHs are also able to catalyze the reverse reaction, that is, oxidation of alcohols into the corresponding aldehydes (Edenberg & McClintick, 2018). Several members of ADH, AKR, CBR, and SDR were detected in saliva and the oral epithelium (Table 1). Concerning the AKR family, it is worth noting the presence of certain isoforms specific to steroid biosynthesis (AKR1C group) in saliva, as their involvement in the metabolism of aroma compounds cannot be excluded. The role played by isoforms from the AKR1A and AKR1B groups in the detoxification of reactive food aldehydes in the intestine has been reported (Barski et al., 2008; Zhong et al., 2009). The presence of these groups in the oral cavity suggests that detoxification activity is initiated immediately upon entrance of aldehydes in the digestive tract. AKR1B1 and AKR1B10 were also reported to metabolize glutathionyl compounds (Shen et al., 2011), suggesting that the reduction of carbonyl compounds after their conjugation by phase II enzymes is possible. Moreover, several works have observed the reduction or oxidation of food aldehydes in the presence of saliva or oral cells (Buettner, 2002a; Muñoz-González et al., 2018; Ployon, et al., 2020) and appeared to be dependent on the NADP content (Muñoz-González et al., 2018).

3.1.3 | Cytochrome P450, flavin monooxygenase, and NADPH-quinone oxidoreductase

Several CYP450 isoforms were found in the selected proteomes. CYP450s represent a family of enzymes known to react with many substrates and play a major role in the detoxification of various compounds via their oxidation process (Guengerich et al., 2016). In rats, CYP450s have been identified in the olfactory mucosa, and their ability to metabolize aroma compounds, such as coumarin and quinoline, was shown (Thiebaud et al., 2013). In humans, the presence of CYP450s was demonstrated by immunohistochemistry in the parotid glands (Kragelund et al., 2008), and their activity was confirmed for certain isoforms in oral tissues (Vondracek et al., 2001). In the latter study, the metabolization activity of CYP450s in the mouth was reported for carcinogenic substances and drugs (polycyclic hydrocarbons and nitrosamines). The activity of CYP450s toward aroma compounds has not been documented to the best of our knowledge. Nevertheless, all these observations suggest that aroma compounds can be metabolized by CYP450 enzymes at the oral level. Similarly, FMOs catalyzing the monooxygenation of sulfur and amine compounds (Krueger & Williams, 2005) and NQOs catalyzing the reduction of quinone compounds (Bianchet et al., 2004) could also be involved in the oral metabolism of aroma compounds belonging to these chemical families. Notably, an increase

in the expression of NQO1 (DT-diaphorase) in saliva following the intake of coffee and broccoli has been reported (Sreerama et al., 1995). This observation emphasizes the importance of diet on the enzymatic equipment present in the oral cavity and suggests that the enzyme content of saliva is dynamically adapted to specific reactive compounds.

3.2 | Transferases

These enzymes catalyze transfer reactions of hydrophilic groups and are generally involved in facilitating the solubilization of metabolized products (Jancova et al., 2010). All families of transferases were represented in the salivary proteomes (Table 2), namely: arylamine *N*-acetyl transferase (NAT), GST, methyltransferase (MT), sulfotransferase (SULT), and UGT. Some isoforms of the GST, UGT, and MT families have also been identified in the oral mucosa (Table 2, asterisks).

3.2.1 | Glutathione transferase

GSTs form a large family of transferases that catalyze glutathione (GSH) transfer reactions on generally hydrophobic substrates (Hayes et al., 2005a). GSH is a tripeptide carrying a free thiol on its cysteine residue and a major physiological reducing agent. Cytosolic GSTs are classified into several families named by Greek letters (e.g., GST Alpha 1, abbreviated GSTA1; Mannervik et al., 2005). The different classes of GST show substrate overlap, enabling the management of numerous compounds of various chemical families (Hayes et al., 2005b). It should be noted that certain GSTs also have a noncatalytic binding function called the ligandin function, enabling the transport or scavenging of small molecules (Oakley et al., 1999). The analysis of proteomes suggests the presence of alpha, kappa, mu, omega, pi, and theta classes in saliva. The induction of alpha, mu, and pi classes in saliva after the consumption of coffee or broccoli has been shown previously (Sreerama et al., 1995). It is important to reiterate in this context that the expression of GST is induced by certain compounds, such as the isothiocyanates contained in Brassicaceae (Kumari et al., 2016; Nakamura et al., 2000). Concerning GSTP1, its expression is particularly high in saliva, exhibiting a production of approximately 1.2 mg/day in human adults, probably secreted by the salivary glands (Fabrini et al., 2014). GSTP1 is inactivated by an antimicrobial salivary compound, hypothiocyanite, and maintenance of its activity requires the presence of a reducing agent (Fabrini et al., 2014). A recent study demonstrated the presence of GSTA1 and GSTP1 in the olfactory epithelium and the GSH conjugation activity of several odorant molecules, such as cinnamaldehyde (X-ray structure shown in Figure 3), carvone, or hydroxynonenal, suggesting a role in periolfaction (Schwartz, Menetrier, et al., 2020). Notably, these two enzymes were also determined to be involved in the olfactory metabolism of aldehyde 2-methylbut-2-enal, an odorant with pheromone (mammary pheromone) properties in newborn rabbit olfactory epithelium (Robert-Hazotte, Faure, et al., 2019). As conjugation improves solubility while forming nonodorant products (Winter et al., 2011), the presence of GSTs in saliva may decrease the amount of aroma molecules that can reach the olfactory epithelium.

3.2.2 | UDP-glucuronosyl transferase

The second major family identified is that of the UGTs. These enzymes catalyze the transfer of a glucuronosyl moiety from UDP-glucuronate to an acceptor containing a carbonyl, hydroxyl, thiol, or amine functional group (Lv et al., 2019; Rowland et al., 2013). This reaction enables the solubilization of potentially toxic molecules to facilitate their elimination. The superfamily of UGTs is divided into five families that differ particularly in their substrate specificity, even if overlap exists. The members found in oral proteomes are essentially of the UGT1A class, which can recognize drug-like substrates, as well as fatty acids, bilirubin, phenols, and sulfur compounds (Rowland et al., 2013; Table 2). UGTs are transmembrane enzymes found in the membrane of the endoplasmic reticulum, nucleus, and plasma membrane. At the olfactory level, in addition to the identification of different classes (Heydel et al., 2016), the participation of UGTs in the termination of the odorant signal has been demonstrated by the decrease in the volatility of aromatic alcohol-type odorant compounds (e.g., eugenol and guaiacol; Lazard et al., 1991). Conjugation would result in a decreased response at the olfactory level, as also previously reported in rats (Thiebaud et al., 2013). At the oral level, UGTs have been found in the cells of the oral epithelium and are active in the metabolism of food compounds, such as polyphenols, some of which are odorant (Mallery et al., 2011).

3.2.3 | Methyltransferase

Methyltransferases catalyze methyl group transfers from the *S*-adenosyl methionine (SAM) cofactor to various compounds having an *O*, *N*, or *S* acceptor atom. Mallery et al. (2011) have demonstrated the presence and activity of catechol *O*-methyltransferase (COMT) in the oral epithelium and salivary glands. COMT could metabolize phenols in the mouth, given its spectrum of activity (Weinshilboum et al., 1999). Other methyltransferases have been identified: thiopurine *S*-methyltransferase (TSMT) and histamine

N-methyltransferase (HNMT), which can methylate sulfur compounds or amines, respectively, (Weinshilboum et al., 1999). Aroma compounds that could be substrates for these enzymes would be metabolized into methylated compounds, which have different properties, such as volatility and/or odorant properties, compared to their precursors. For instance, Ijichi et al. (2019) found that 2-furfuryl thiol (2-FT; boiling point: 147°C at 12 mm Hg; vapor pressure: 3.98 mm Hg at 25°C; odor type: coffee) was metabolized to furfuryl methyl sulfide (FMS; boiling point: 64°C–65°C at 15 mm Hg; vapor pressure: 1.58 mm Hg at 25°C; odor type: alliaceous/sulfurous) following incubation with saliva as well as in the oral cavity.

3.2.4 | Sulfotransferase

SULTs act by transferring a sulfonyl group to a hydroxyl or amine group using the 3′-phosphoadenosine-5′-phosphosulfate cofactor (PAPS) as the donor (Gamage et al., 2006). Similar to GSH or glucuronate transfer, sulfonyl transfer improves the water solubility of the formed product. Two isoforms of SULTs were detected in saliva: SULT1A1 and SULT2B1. However, the presence of SULTs has not been reported in the oral mucosa based on immunohistochemistry experiments (Mallery et al., 2011) or in the buccal proteome that was analyzed. SULT1A1 is capable of handling various phenols by conjugating a sulfonyl on the alcohol function (Gamage et al., 2006). Hydroxy methyl furfural, an aroma compound, was shown to be sulfoconjugated by SULTs (Sachse et al., 2016).

3.2.5 | Acetyl transferase

Arylamine N-acetyltransferase (NAT) is the only acetyl transferase present in the salivary proteomes analyzed. NAT1 catalyzes the transfer of acetyl groups from acetyl coenzyme A to the nitrogen atom of various cyclic arylamines, thus generating the corresponding arylamides (Sim et al., 2014). Among the substrates of NAT1, numerous arylamine environmental contaminants can be cited such as aniline and alkylaniline (Liu et al., 2007). Acetyl transfer is considered to be a detoxification step, as it decreases the concentration of substrates, which metabolic hydroxylation of primary amino group generates toxic *N*-arylhydroxylamines (Liu et al., 2007). Given the toxicity and mutagenicity of heterocyclic arylamines, which can be formed during food pyrolysis (Choi et al., 2006; Felton & Knize, 1990), NAT could be important for early detoxification of arylamine in the oral cavity, although, to our knowledge, there is no study that has been carried out in this context.

3.3 | Hydrolases

Hydrolases are enzymes that catalyze the dissociation of covalent bonds using a water molecule. Some hydrolases are involved in the detoxification processes such as esterases (Ross & Crow, 2007). Interestingly, previous work indicated possible metabolization of aroma esters by salivary esterases (Buettner, 2002b; Pérez-Jiménez et al., 2020). Thus, we explored oral proteomic data to identify such enzymes. It includes notably CES and PON (Table 3). CAs also have esterase activity and will be discussed further later. Salivary true lipases are not considered in this review because they hydrolyze the ester bonds of long-chain triacylglycerols and have been proposed to be involved in fat perception (Pepino et al., 2012) but are unlikely to be involved in the metabolism of molecules of lower molecular weight such as aroma compounds. Historically, esterase activity has been measured in saliva with common laboratory substrates (thiophenyl acetate and thiophenyl butyrate; Lindqvist & Augustinsson, 1975) but also more recently with aroma compounds, such as aliphatic or aromatic esters (Buettner, 2002b; Genovese et al., 2009; Muñoz-González et al., 2019; Pérez-Jiménez et al., 2020; Perez-Jimenez et al., 2019).

3.3.1 | Carboxyl esterase

CESs (for the crystal structure of CES1, see Figure 3) can hydrolyze esters but also amides and lipids (Pindel et al., 1997). Among the CESs, the CES2 isoform is of particular interest because the metabolic activity of the homologue enzyme from mice modulates the activation of an olfactory receptor in vitro (Kida et al., 2018).

3.3.2 | Paraoxonase

Paraoxonases (PONs) were also found in saliva but not in the oral epithelium proteome that was analyzed. These enzymes hydrolyze esters, such as phenyl acetate, but also have the notable property of hydrolyzing many aliphatic and aromatic lactones (Draganov et al., 2005). Research on the role of salivary PONs in the metabolism of lactones should be conducted in the future, as lactones are an important class of aroma molecules (Dufosse et al., 1994; Maga & Katz, 1976).

3.3.3 | Carbonic anhydrase

CAs, which are known primarily for their ability to buffer salivary medium by modulating the carbon dioxide/carbonic acid balance, include catalysts that are also capable of hydrolyzing esters (Supuran, 2008). Several CA

isoforms are present in saliva, and some are also present in the oral epithelium (Table 3). CA6 is the major isoform secreted by the salivary glands as a defense protein (Kivela et al., 1999). It has even been suggested that the total esterase activity of saliva is largely derived from CA6 (Tecles et al., 2016), although in this study, only one substrate (4-nitrophenyl acetate) was considered.

3.3.4 | Epoxide hydrolase

EPHXs were identified in the salivary proteomes only. These enzymes catalyze the hydrolysis of molecules containing the highly reactive epoxide group into their corresponding diols (Morisseau & Hammock, 2005). Indeed, EPHX1 was shown to convert various epoxides such as styrene oxide, 1-methyl-1-phenyloxirane, indene 1,2-oxide, and cyclohexene oxide (Václavíková et al., 2015). EPHX3 was shown to have high affinity and catalytic efficacy for fatty acid epoxides (Decker et al., 2012). These reactive molecules can be found in food (Manson, 1980) and some epoxides are aroma compounds, notably glycidate esters also known as oxiranes (Zviely, 2005). EPHX have not been studied in the oral context to our knowledge and further work is needed to claim any reactivity with aroma epoxides.

4 | WHAT ARE THE CONDITIONS ENABLING METABOLIZING ENZYMES TO BE ACTIVE IN SALIVA?

It can be reasonably assumed that the enzymes identified are most likely active in the cellular context of the oral mucosa, as demonstrated for several of them in previous studies (Mallery et al., 2011; Ployon, Brule, et al., 2020). However, the activity of enzymes in saliva is worthy of discussion, although historically, many enzymes active in a salivary context have been identified (Chauncey, 1961; Chauncey et al., 1954; Giebultowicz et al., 2009; Nickerson et al., 1957; Sreerama et al., 1995). To maintain their activity, enzymes need specific conditions, that might be altered by the presence of food in the mouth. Therefore, different systems are present in saliva to regulate the variation of these conditions. Some of the factors affecting these conditions are discussed in the following paragraph.

4.1 | pH and temperature

The pH of saliva is between 6.2 and 7.4 (Schipper et al., 2007), which is a condition compatible with the majority of human enzymes, enabling them to retain their three-dimensional structure necessary for their catalytic function. Although saliva has an efficient buffering capacity due to enzymatic systems, such as CAs that can maintain pH by modulating the carbon dioxide/carbonic acid balance (Kivela et al., 1999), it should be noted that temporary but abrupt changes in pH can occur. For instance, the ingestion of acidic foods, such as soft drinks, wine or certain cheeses, or the consumption of sweet foods promoting the development of bacteria that produce acidic metabolic compounds (lactic and butyric acids; Schwartz, Canon, et al., 2021) may affect the pH of the oral cavity and thus the activity of enzymes.

The temperature of the oral cavity is 36°C and varies extremely slightly (Moore et al., 1999). This temperature corresponds to an optimum for many salivary enzymes, and because of its stability, it is not a regulating/modulating factor for these activities. Under certain consumption conditions (hot or cold food), this temperature can vary significantly over a very short period of time (Barclay et al., 2005) and can therefore briefly affect the activity of certain enzymes, especially those having a high velocity (Schneyer, 1951).

4.2 | Cofactors

The documented presence of most enzyme cofactors in saliva indicates that the enzymes functioning with cofactors are likely to be active in saliva. GSH is present in saliva at a concentration close to mM (Tothova et al., 2015), enabling GSH-dependent enzymes to function (GSH-transferases and GSH-peroxidase). Interestingly, the presence of GSH reductase (Sivadasan et al., 2015) in salivary proteomes suggests the possibility of regeneration of oxidized GSH to reduced GSH in saliva. NADH and FAD cofactors are also present in saliva (Kumar et al., 2018). NAD(P)H enables the functioning of many families of salivary oxidoreductases (Table 1). It should be noted that NAD(P)H is subjected to oxidation to $NAD(P)^+$ by the action of lactoperoxidase, generating the hypothiocyanite ion during the elimination of H_2O_2 (Hogg & Jago, 1970). A large number of molecules and enzymes intervene to maintain the salivary redox balance (Schwartz, Neiers, et al., 2020, 2021). Depending on the concentration of the oxidized or reduced form of the NAD(P)H cofactor, the reactions involved may be affected in one direction or the other (oxidation or reduction). Data reporting the presence of cofactors acetyl-CoA, pyridoxal phosphate (PLP), PAPS, and SAM in saliva are scarce. The release of these cofactors in saliva could occur during lysis of desquamated epithelial cells or oral bacteria, as well as from food, as some of them are formed from vitamin precursors (e.g., vitamins B5 and B6). It is also conceivable that some salivary enzymes

are already complexed with their cofactor, especially in the case of covalent binding, as with cysteine-conjugate beta lyases (CCBLs) covalently bound to PLP (Cooper et al., 2011). It is important to consider that saliva is continuously secreted into the oral cavity, while several factors have been reported to modulate the salivary flow. Stimulations, such as mastication or sensory food cues (Morquecho-Campos et al., 2020), increase secretion of saliva, especially the contribution of the parotid glands (Dawes et al., 2015; Mackie & Pangborn, 1990), which influences the enzymatic composition and concentration (Dawes, 1969) and thus reactions occurring in the mouth. For instance, basic proline-rich proteins, which scavenge tannins to prevent them from interacting with other proteins, such as digestive enzymes, are only secreted by the parotid glands (Shimada, 2006). Thus, to consider the composition of saliva during food consumption it is important to carry out in vivo studies in conditions close to consumption, but also to perform research on the salivary factors affecting the activity of oral enzymes.

4.3 | Partner proteins or enzymes

Some XMEs require the presence of partner enzymes. For example, CYP450s require the presence of NADPH-CYP450 reductase, which is necessary for electron transfer during the oxidation mechanism (Guengerich et al., 2016). This enzyme is present in saliva (Pappa et al., 2018), suggesting that CYP450s should be functional in this fluid. The inactivation of salivary GSTP1 by salivary hypothiocyanite has been documented to cause the oxidation of exposed cysteine residues (Fabrini et al., 2014). Oxidations linked to exogenous molecules may also occur during food intake. Therefore, it is important to point out the role of redox maintenance proteins ensuring the regeneration of salivary thiol proteins (for a complete review, see Schwartz, Neiers, et al., 2021). More generally, the antioxidant capacity of saliva plays a major role in the functioning of oral enzymes and influences the ability of saliva to metabolize flavor compounds (Muñoz-González et al., 2018; Piombino et al., 2014).

4.4 | Substrate and inhibitor concentrations

The presence in the mouth of different potential substrates for one XME can lead to competition between all substrates, regardless of whether they come from food or are endogenous compounds. This competition can lead to a decrease in the velocities of enzymatic reactions by various mechanisms (competitive, noncompetitive, and incompetitive inhibition). For instance, the intake of a drug during a meal may saturate the corresponding XMEs, thereby leading to a decrease in the quantity of aroma molecules metabolized by these XMEs. Also, inhibitors of enzymatic activity can also be present in the diet. For instance, a plant-based diet includes the consumption of tannins, which participate in plant defense mechanisms. Tannins are known to inhibit the enzymes of the digestive tract due to their ability to interact with and aggregate proteins (Canon et al., 2013; Ployon et al., 2018). Thus, it is likely that tannins also inhibit the activity of XMEs as reported for phase-I and phase-II reactions (Krajka-Kuźniak, 2003). Nevertheless, studies on the effect of food matrix components on the activity of oral enzymes are scarce.

5 | ORAL METABOLIZATION OF AROMA COMPOUNDS AND PUTATIVE ENZYMES INVOLVED

The presence of saliva or oral mucosa has been demonstrated to affect the release of several classes of aroma compounds known to be substrates of XMEs, namely, aldehydes, ketones, esters, and thiols. A pioneering study using gas chromatography/mass spectrometry (GC/MS), which was conducted by Buettner in 2002, demonstrated the reduction of these compounds within minutes of incubation with fresh saliva (Buettner, 2002a, 2002b). The metabolization of these compounds leads to the formation of compounds belonging to different chemical families and having sensory properties differing from those of precursor compounds (Table 4, Figure 4). Accordingly, in nasal tissue, a rapid synthesis of metabolites resulting from odorant metabolism and having odorant properties was recently shown (Robert-Hazotte, Schoumacker, et al., 2019). Alternatively, a precursor may not be sensorially active, while its metabolite may be. For instance, glycoside conjugates (Muñoz-González et al., 2015) and cysteine conjugates (Starkenmann et al., 2008) can be metabolized by enzymes classified beyond the XME group with probably a microbial origin.

5.1 | Aldehydes

In the case of aldehydes, their disappearance was correlated with the appearance of their corresponding alcohols, suggesting their reduction by salivary enzymes. This effect was observed for short chain aliphatic aldehydes (hexanal, methional, octanal) and aromatic aldehydes (phenylacetaldehyde) in the presence of saliva (Buettner, 2002a; Ijichi et al., 2019; Muñoz-González et al., 2018; Muñoz-González et al., 2019). Two aldehydes with longer

TABLE 4 Aroma molecules or precursors significantly affected by the presence of saliva or oral mucosa, detected metabolites and candidate corresponding enzymes

Chemical family	Compound	Flavor properties	DT (mg/kg)	Food example	Detected metabolite	Flavor properties	DT (mg/kg)	Reactions	References	Candidate enzyme families
Aldehydes	Hexanal	Grassy	0.0075	Black walnut	Hexanol	Green	0.7	Reduction	(Buettner, 2002a; Ijichi et al., 2019; Muñoz-González et al., 2018)	AKR, CBR, SDR, GST
	Methional	Cooked potato	0.00004	Potato	Methionol	Onion	0.0002		(Buettner, 2002a)	
	Phenylacetaldehyde	Honey-like	0.009	Tomato	Phenylethanol	Floral	0.045		(Buettner, 2002a)	
	Benzaldehyde	Fruity	0.3	Almond	Benzyl alcohol	Fruity	5.5		(Muñoz-González et al., 2018)	
	Octanal	Green grassy	0.0007	Pili nut	Octanol[a]	Green	0.054		(Buettner, 2002a; Muñoz-González et al., 2018)	
	Octenal	Fatty	0.003	Fruits	2-Octen-1-ol	Fatty	0.04		(Muñoz-González et al., 2018)	
					1-Octanol	Green	0.054		(Muñoz-González et al., 2018)	
	Nonanal	Citrus-like	0.0035	Corns	ND				(Buettner, 2002a)	
	Decanal	Citrus-like, soapy		Lime	ND				(Buettner, 2002a)	
	Trans-2-hexen-1-al	Green	0.04	Tomato	Hexenoic acid	Acidic		Oxidation	(Ployon, Brule, et al., 2020)	ADH, ALDH, AKR, CYP
Ketones	Pentan-2,3-dione	Toasted	0.005	Cocoa	2-Hydroxy-pentan-3-one	Truffle		Oxidation/ reduction	(Muñoz-González et al., 2018; Ployon, Brule, et al., 2020)	AKR, CBR, SDR
					3-Hydroxy-pentan-2-one	Creamy			(Muñoz-González et al., 2018; Ployon, Brule, et al., 2020)	
	Butane-2,3-dione	Buttery	0.0023	Butter	3-Hydroxy-butan-2-one	Creamy	0.8		(Muñoz-González et al., 2018)	
	1-Octen-3-one	Earthy	0.000007	Fruits	3-Octanone	Mushroom	1		(Muñoz-González et al., 2018)	
					1-Octen-3-ol	Mushroom	0.007		(Muñoz-González et al., 2018)	
	Nonan-2-one	Cheesy	0.05	Banana	Nonan-2-ol	Waxy	0.28		(Ployon, Brule, et al., 2020)	

(Continues)

TABLE 4 (Continued)

Chemical family	Compound	Flavor properties	DT (mg/kg)	Food example	Detected metabolite	Flavor properties	DT (mg/kg)	Reactions	References	Candidate enzyme families
	Decan-2-one	Fermented	0.009	Corn	Decan-2-ol	Waxy	0.33		(Ployon, Brule, et al., 2020)	
Esters	Ethyl butanoate	Fruity	0.001	Grapefruit juice	ND			Ester hydrolysis	(Buettner, 2002b; Perez-Jimenez et al., 2019)	CES, PON, CA
	Ethyl pentanoate	Fruity	0.094	Wine	ND				(Perez-Jimenez et al., 2019)	
	Ethyl hexanoate	Fruity	0.008	Orange juice	Hexanoic acid[b]	Cheesy	0.2		(Buettner, 2002b; Perez-Jimenez et al., 2019; Ployon, Brule, et al., 2020)	
	Ethyl octanoate	Waxy	0.02	White wine	Octanoic acid[b]	Soapy	0.5		(Buettner, 2002b; Perez-Jimenez et al., 2019)	
	Ethyl decanoate	Waxy	0.02	Sweet and sour cherry	Decanoic acid [b]	Soapy	0.7		(Perez-Jimenez et al., 2019)	
	Isoamyl acetate	Fruity	0.005	Banana	ND				(Perez-Jimenez et al., 2019)	
	Benzyl acetate	Fruity	0.002	Apple	Benzyl alcohol	Fruity	5.5		(Ijichi et al., 2019)	

(Continues)

TABLE 4 (Continued)

Chemical family	Compound	Flavor properties	DT (mg/kg)	Food example	Detected metabolite	Flavor properties	DT (mg/kg)	Reactions	References	Candidate enzyme families
Glycoconjugates	Guaiacol primeveraside	No flavor		Grapes	Guaiacol	Woody	0.00075	Glycosidic bond hydrolysis	(Mayr et al., 2014)[c]	Glycosidases
	m-Cresol glucoside	No flavor		Grapes	m-Cresol	Phenolic	0.085		(Mayr et al., 2014)[c]	
	Syringol glucoside	No flavor		Grapes	Syringol	Medicinal	0.4		(Mayr et al., 2014)[c]	
	Syringol gentiobioside	No flavor		Grapes	Syringol	Medicinal	0.4		(Mayr et al., 2014)[c]	
	Guaiacol glucoside	Smoky	0.07	Grapes	Guaiacol	Smoky	0.00075		(Parker et al., 2020)[c]	
	Geranyl glucoside	Floral	1.6	Grapes	Geraniol	Floral	0.004		(Parker et al., 2020)[c]	
	Cyanidin 3-sambubioside	No flavor		Black elderberries	Cyanidin 3-sambubioside glucuronide	ND		Glucuronide conjugation	(Mallery et al., 2011)	UGT
Cysteine S conjugates	*S*-(R/S)-3-(1-hexanol)-L-cysteine	No flavor		Grapes	(R/S)-3-sulfanylhexan-1-ol	Sulfurous	0.000017	Cys-conjugate lyase	(Starkenmann et al., 2008)[c]	CCBL
	S-(1-propyl)-L-cysteine	No flavor		Onion	1-Propanethiol	Alliaceous	0.00006			
	S-((R/S)-2-heptyl)-L-cysteine	No flavor		Bell pepper	2-Heptanethiol	Sulfurous	0.003			
Thiols	Phenyl ethanethiol	Sulfurous		Roasted sesame	ND			Oxidation, conjugation	(Buettner, 2002b)	Oxidoreductases, transferases
	3-Mercapto-3-methyl-1-butanol	Catty	0.0013	coffee	ND				(Buettner, 2002b)	
	2-Furfurylthiol	Meat like	0.00004	Coffee	Furfuryl methyl sulfide	Sulfurous	0.00004	Methyl-conjugation	(Buettner, 2002b; Ijichi et al., 2019)	

Abbreviations: DT, detection threshold in water; ND, not determined.

[a]Formation of metabolites improved by adding cofactor NADH.

[b]Metabolites not formed in presence of an esterase inhibitor.

[c]Evidences for microbial enzymes involved.

Source: Detection threshold were extracted from Gemert (2003). Descriptors of flavor properties were retrieved from the Good Scent Company database (http://www.thegoodscentscompany.com).

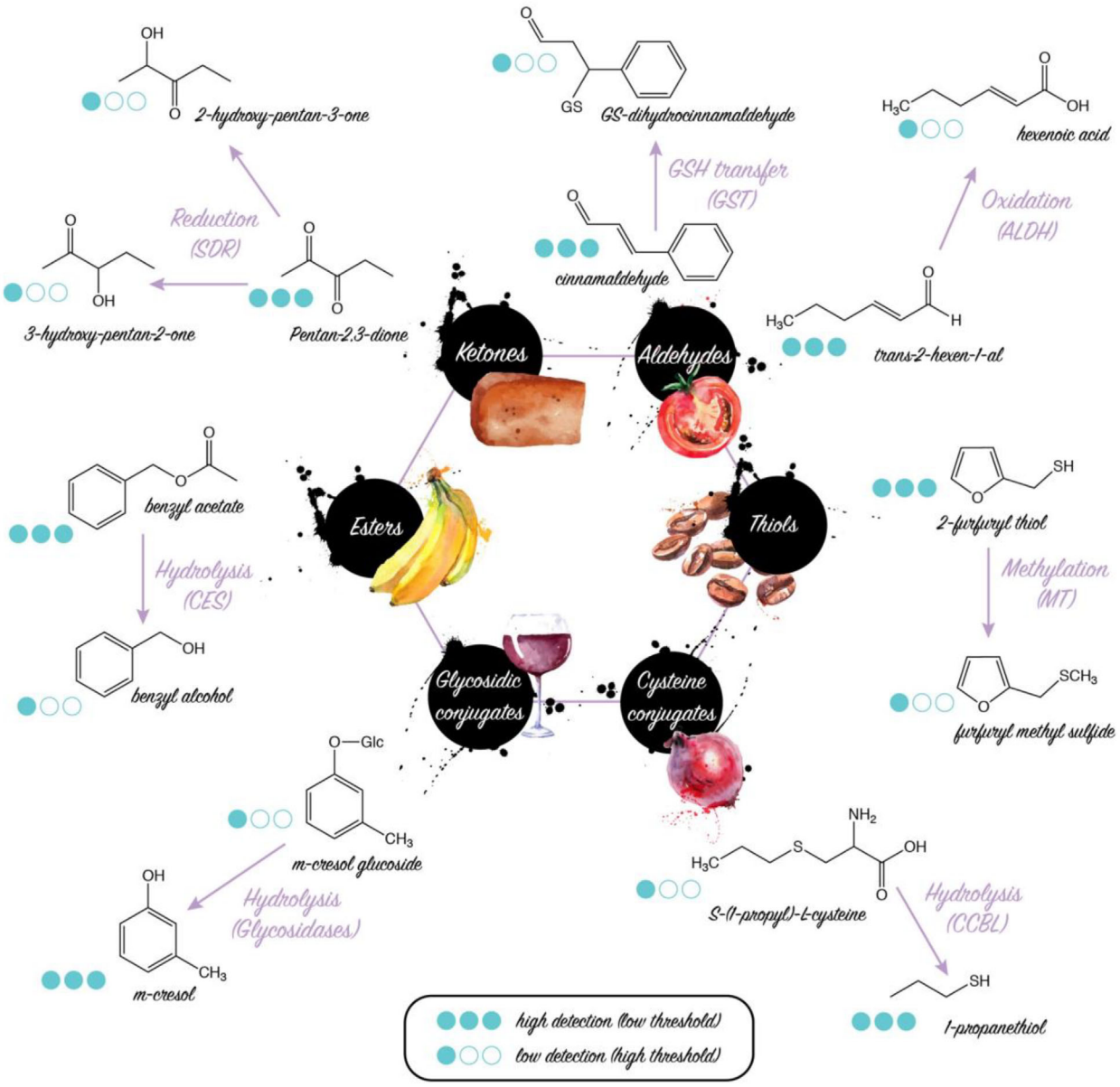

FIGURE 4 Aroma metabolization involving XMEs in the oral cavity. Metabolization reactions observed from studies on saliva and oral epithelium showing the aroma compounds, their metabolites, representative XMEs and possible microbial enzymes. Variations of detection thresholds between aroma molecules and their corresponding metabolites have been represented with a scale (one dot, low detection; three dots, high detection)

aliphatic chains (nonanal and decanal) were also investigated (Buettner, 2002a). However, the decreases in the levels of these aldehydes were not associated with the appearance of metabolites, suggesting that hydrophobic interactions with salivary proteins, such as mucins, can also occur and impact aroma release (Pages-Helary et al., 2014). Another reported case concerns trans-2-hexen-1-al. The oxidation of this compound to hexenoic acid was noted by Ployon, Brule, et al. (2020) in the presence of a model of oral mucosa. More globally, Muñoz-González et al. (2018) demonstrated that metabolization phenomena were correlated with salivary protein concentration and salivary antioxidant potential. Furthermore, in this study, the addition of NADH cofactor increased the reduction of octanal to octanol by saliva. This observation strongly suggests the involvement of NAD(P)H-dependent enzyme systems. Different oxidoreductases present in the oral cavity and identified from proteomic data analyzed in this review (Table 1) are able to catalyze these reactions, as described above (ADH, ALDH, AKR, CBR, SDR, and CYP450). Dedicated studies are warranted to decipher which enzyme(s) is (are) involved in these activities.

5.2 | Ketones

For ketones, reduction reactions were primarily observed in the presence of oral mucosa (Table 4; Ployon, Brule, et al., 2020). Monoketones such as 2-pentanone and 2-octanone were not found to be metabolized, however diketones such as 2,3-butanedione and 2,3-pentanedione were metabolized in presence of saliva (Muñoz-González et al., 2018). The particular case of pentan-2,3-dione is interesting. This compound is metabolized to two possible products, 2-hydroxy-pentan-3-one and 3-hydroxy-pentan-2-one, and this mechanism echoes a similar observation (Zaccone et al., 2015). In this case, metabolic activity was observed in the presence of human bronchial/tracheal epithelial cells and was attributed to the dicarbonyl and xylulose reductase (DCXR) enzyme (Zaccone et al., 2015). Additionally, in the olfactory epithelium, the rapid synthesis of these metabolites also involves DCXR activity (Robert-Hazotte, Schoumacker, et al., 2019). This enzyme is also detected in saliva (Table 1). Other enzymes were also observed to metabolize ketones, including the potential aldehyde reductases (AKR, CBR, and SDR) identified in the previous paragraph.

5.3 | Esters

In the case of esters, Buettner demonstrated the disappearance of ethyl butanoate, ethyl hexanoate, and ethyl octanoate after incubation with fresh saliva (Buettner, 2002b) and the correlated production of the corresponding carboxylic acids (Pages-Helary et al., 2014). In a study on the impact of saliva on wine aroma molecules, it was shown that the concentration of total esters in wine headspace decreased in the presence of human saliva (Genovese et al., 2009). This effect was determined to be more pronounced with white wine than with red wine; thus, the authors suggested that the presence of tannins in red wine can explain this difference due to their ability to inhibit enzymatic activity. In 2019, Perez-Jimenez showed the degradation of a series of esters by the enzymatic action of fresh saliva (Table 4). A metabolizing effect, coinciding with the appearance of the corresponding carboxylic acids, was shown for ethyl hexanoate, ethyl octanoate, and ethyl decanoate (Perez-Jimenez et al., 2019). This effect was inhibited in the presence of $CaCl_2$, an esterase inhibitor, confirming their role in ester metabolization. Another study reported the metabolism of benzyl acetate to benzyl alcohol in the presence of saliva and nasal mucus (Ijichi et al., 2019). The conversion of ethyl hexanoate to hexanoic acid was also shown in the presence of an oral mucosa model (Ployon, Brule, et al., 2020). As suggested earlier, different esterases could be involved in these metabolic phenomena (CES, PON, CA).

5.4 | Thiols

Concerning thiol-type aroma molecules, a prior study has shown their decrease in the presence of saliva (Buettner, 2002b). It must be kept in mind that thiols have particularly low detection thresholds and thus have a strong contribution to perception (Table 4). Various oxidoreductases present in saliva can oxidize thiols. In addition, it has been suggested that salivary peroxidases may also be involved (lactoperoxidase and myeloperoxidase; Buettner, 2002b). Sulfur-containing aroma molecules, such as disulfide compounds, could be substrates for thiol-transferases, such as thioredoxin, glutaredoxin, or GST omega. Furthermore, the metabolism of thiol compounds may also occur through conjugation via certain transferases, such as UGT, GST, or TPMT. In a recent study, the in-mouth metabolization of 2-FT to FMS was reported (Ijichi et al., 2019). Ijichi et al. (2019) attributed this biological reaction, which is known to occur in mammals and microorganisms, to the activity of a methyltransferase. Methyltransferase catalyzes the transfer of methyl groups from a primary methyl donor, such as *S*-(5′-adenosyl)-L-methionine (SAM), to a thiol group. Among methyltransferases, TPMT is a potential candidate, as it is known to be active on various thiols (Wu et al., 2019) and is present in saliva (Table 2).

5.5 | Cysteine conjugates and glycoside conjugates: Evidence for microbial enzymes

Two other classes of compounds have been reported to be subject to oral metabolization: cysteine conjugates and glycoside conjugates. For these two classes of compounds, the precursors are not sensorially active per se. However, the compounds formed after metabolization in the mouth can be aroma compounds. Although the enzymes that are expected to catalyze these reactions are not XMEs, they are briefly described below to provide a more complete view of the enzymatic reactions that can occur in the oral cavity.

5.5.1 | Cysteine conjugates

Cysteine conjugates are compounds typically found in garlic and onion but also in some white wines, such as Sauvignon Blanc (Tominaga et al., 1998). The metabolism of cysteine conjugates leads to the production of compounds with a free thiol function, which are therefore very fragrant

(Starkenmann et al., 2008). In the latter study, a contribution of the oral microbiota to this metabolization was demonstrated, notably by the action of the anaerobic bacterium *Fusobacterium nucleatum*. The formation of sulfur compounds after metabolization in the presence of saliva was also shown in cabbage extracts (Frank et al., 2018). The enzymes responsible for this activity are probably CCBL enzymes capable of catalyzing the dissociation of the C–S bond between the C_β and S_γ atoms of cysteine, thereby generating free thiols without cysteine groups. CCBLs catalyze the beta-elimination of cysteine conjugates having an electrophilic group on the sulfur atom, utilizing the PLP cofactor converted to pyridoxamine phosphate for catalysis (Cooper & Pinto, 2006). CCBLs are typical of some anaerobes of the oral cavity but could also be of human origin. Indeed, the presence of human transaminases has been identified in saliva, and these enzymes exhibit cysteine–thiol lyase activity (Cooper & Pinto, 2006). Aspartate aminotransferases (encoded by the GOT1 and GOT2 genes), as well as kynurenine-oxoglutarate transaminase 3 (encoded by the KYAT3 gene), were detected in saliva (and in the oral epithelium for GOT1 and GOT2; Denny et al., 2008; Ghosh et al., 2012; Grassl et al., 2016; Pappa et al., 2018; Sivadasan et al., 2015) and may also be involved in cysteine conjugate metabolization as previously shown (Cooper & Pinto, 2006).

5.5.2 | Glycoside conjugates

Glycoside conjugates constitute a class of compounds commonly found in various plant-derived foods and exposed to metabolization by salivary enzymes. This metabolization generally involves the hydrolysis of the sugar group by glycosidases (Walle et al., 2005). Beyond the well-known glycosylated polyphenols, such as flavonoids and anthocyanins that have bitter taste properties (Roland et al., 2013), which are outside the scope of the present paper focused on aroma compounds, some simple phenols may also have odorant properties. These properties are observed for the phenol glycosides present in certain wines with a smoky taste produced from berries harvested near burnt forests (Mayr et al., 2014). Metabolization by glycosidases releases free phenols (guaiacol, cresol, and syringol), which have "smoky"-type sensory properties. Other enzymatic products with odorant properties resulting from the deglycosylation of their precursors have been identified, such as terpenes, benzene derivatives, and alcohols (Muñoz-González et al., 2015). In saliva, a bacterial origin of glycosidase activity has been suggested, although it is significant only after several days of reaction (Muñoz-González et al., 2015), raising questions regarding their contribution to the perception of a food during the time of its consumption. The existence of human glycosidase activity in saliva (Stradwick et al., 2017) and the oral epithelium (Mallery et al., 2011; Walle et al., 2005) should also be further investigated. This activity is believed to come from human beta-glucosidase (encoded by GBA3), which is present in the mouth (Ghosh et al., 2012) and is known to participate in the in vivo metabolism of certain glycosylated derivatives (Nemeth et al., 2003).

6 | DISCUSSION

Reactive compounds must be addressed as soon as possible after their entrance into the organism. As a result, XMEs actively participate in the detoxification of xenobiotics in the oral cavity. Aroma compounds are generally hydrophobic molecules belonging to numerous chemical families with different reactivities. Thus, XMEs are likely to participate in their elimination depending on their chemical structure. However, it was only very recently that studies began to consider their reactivity toward aroma molecules. The aim of this study was to review the existing evidence of the presence of XMEs in the oral cavity (saliva and oral mucosa) as well as pieces of evidence of the oral metabolization of aroma compounds in order to point out the enzymes potentially involved. To this end, we screened five recent proteomes to inventory XMEs among the thousands of proteins present in the oral cavity (Denny et al., 2008; Ghosh et al., 2012; Grassl et al., 2016; Pappa et al., 2018; Sivadasan et al., 2015). Through this study, we identified 91 XMEs among three enzyme superfamilies, namely, oxidoreductases, transferases, and hydrolases. It is important to consider that proteomics enables the identification of proteins but provides no information on their actual activity. Indeed, the identification of a protein may originate from fragments resulting from the lysis of desquamated cells. Nevertheless, the activity of certain enzymes has been documented in the oral cavity, indicating that at least several of these proteins are active in saliva and oral tissues. XMEs are involved in the detoxification of compounds entering the body through food intake, although the role of some XMEs is opposite. For example, ADHs catalyze the oxidation of ethanol to acetaldehyde, a carcinogenic compound actually more harmful than its precursor (Homann et al., 1997). Acetaldehyde can be neutralized by ALDH2, and patients who are heterozygous for its gene have higher levels of acetaldehyde (Väkeväinen et al., 2000). This phenomenon indicates the importance of the complex enzymatic network present in the mouth that can influence the metabolism of compounds entering the oral cavity.

In this regard, it has been reported the metabolism of aroma compounds in the presence of saliva

(Buettner, 2002a, 2002b; Hussein et al., 1983; Muñoz-González et al., 2018; Muñoz-González et al., 2019) or oral cells (Ployon, Brule, et al., 2020; Muñoz-Gonzalez et al., 2021) as well as in vivo conditions (Muñoz-Gonzalez et al., 2021; Ijichi et al., 2019; see Table 4). Aroma compounds participate in the sensory characteristics of food. These compounds are generally present in very small quantities in foods, but they contribute significantly to their quality and acceptability. Regarding their metabolization, the perception thresholds of the initial molecules (XME substrates) are often different (generally lower) than that of the products (Table 4, Figure 4). For example, aldehydes have a perception threshold of 10–100 orders of magnitude below the perception threshold of alcohols, that is, their metabolites. This observation is also true for ketones (metabolized to alcohols) and esters (metabolized to carboxylic acids and alcohols). In other words, oral metabolism leads to the formation of new molecules with higher detection threshold, and therefore, likely to be less perceived than their corresponding precursor. Up to now, most of the works on oral aroma metabolism have been performed using ex vivo conditions that although very relevant have poorly considered the complexity of phenomena occurring in the oral cavity during consumption. To our knowledge, only two studies (Ijichi et al., 2019; Muñoz-Gonzalez et al., 2021) have been carried out in vivo. In a recent study, Ijichi et al. (2019) showed that certain aroma compounds are metabolized in the oral cavity, forming products at a concentration above their detection threshold, which could be perceived by the individual. In addition, Muñoz-Gonzalez and her collaborators coupling both in vivo, in vitro experiments and sensory evaluation have recently studied the effect of oral metabolism of aroma compounds on their persistence, which correspond to the length during which an aroma compounds continue to be release from the oral cavity and be perceived. They demonstrated that the persistence of an aroma compound depends in part on its metabolism in the oral cavity. Thus, the perceived aroma intensity of the compounds that are metabolized in the oral cavity decreases faster than that of the nonmetabolized compounds (Muñoz-Gonzalez et al., 2021). In this study, authors have also shown that aroma compounds adsorb onto the mucosal pellicle as previously reported (Ployon, et al., 2020), while the aggregation of the mucosal pellicle by tannins (Ployon et al., 2018) may disturb these interactions. Thus, while oral metabolism plays a role in aroma persistence, it is not the only mechanism involved. Moreover, these both in vivo studies have been carried out on aroma solutions in water. Thus, future studies that consider more complex food matrices are needed to elucidate the role of oral metabolism on food flavor perception.

Another aspect concerns the influence of the diet on the modulation of XME expression. Indeed, several studies have shown that XMEs can be overexpressed after consumption of certain foods rich in bioactive molecules (Hodges & Minich, 2015) with evidence for salivary XMEs of the GST, ALDH, and NQO families, which are overexpressed after consumption of coffee or broccoli (Sreerama et al., 1995). This finding suggests that dietary habits may alter oral enzymatic arsenal with a potential effect on oral xenobiotic metabolism. Similarly, the well-documented genetic variability of XMEs (Relling & Evans, 2015) could also influence oral xenobiotic metabolism through the absence of a gene or the presence of allelic variants. A last point concerns the role of the oral microbiota. In this study, we focused on human enzymes, but it is important to keep in mind that bacterial enzymes could also contribute to the oral metabolism of aroma compounds. As metaproteomic data of the oral microbiota are scarce or poorly annotated due to the lack of characterization of microbial enzymes, only human enzymes were included in this study. Nevertheless, there is now strong evidence regarding the likely involvement of microbial enzymes such as glycosidases and CCBLs. Notably, these enzymes catalyze reactions leading to the opposite observation concerning detection thresholds: nonodorant precursors result in odorant products after oral metabolization, which balances the trend observed with the other aroma families. In the context of wine, an ex vivo study showed the ability of oral microbiota to produce aroma molecules from grape odorless glycosidic precursors, with large interindividual variability ($n = 3$; Muñoz-González et al., 2015), suggesting that personal biological variabilities can affect the flavor sensing (Frumento, 2018). Future research may investigate the role of the oral microbiota in metabolism affecting the perception of certain aromas.

In conclusion, the enzymes identified in this study based on proteomic data constitute the oral enzymatic detoxification system. These enzymes may assure the handling of exogenous compounds upon entrance in the oral cavity via various possible reactions. Aroma compounds entering the oral cavity during food consumption are potential substrates of this enzymatic system given actual knowledge gained from ex vivo studies. According to pioneer in vivo studies, it seems that this oral metabolism could affect the perception of aroma compounds. Nevertheless, further studies are needed to understand this phenomenon in real food consumption conditions. In addition to the metabolism of aroma molecules, some oral XME are also active on sapid molecules (e.g., oral COMT metabolizes some food flavonoids, molecules with a bitter taste; Mallery et al., 2011). Thus, in addition to investigating their potential role in aroma perception, their putative role in the context of taste compounds metabolization and perception should also be further explored in the future to

gain a deeper understanding of XME activity on flavor perception.

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AUTHOR CONTRIBUTIONS

Mathieu Schwartz drafted the manuscript with input from all authors. Fabrice Neiers, Jean-Philippe Charles, Jean-Philippe Charles, Carolina Muñoz-González, Gilles Feron, Francis Canon, and Mathieu Schwartz revised the manuscript. All authors have approved the submitted version.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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