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Review Article

Thiol sensing: From current methods to nanoscale contribution

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ABSTRACT

Thiols play critical roles in many biologicals processes: they are involved in combating oxidative stress and maintaining redox homeostasis. In agri-food, they are responsible for organoleptic aspect of many foodstuffs. Thus, thiol identification and quantification are challenging due to their similar chemical structures (especially for small/volatile thiols), reactivity and matrices of these compounds. To overcome the analytical issues, many methods and technics were developed each with their own advantages and drawbacks. Lately, one emerging field in analytical development goes through the contribution of nanoparticles. Scientific teams rely on their unique properties to improve sensitivity, selectivity and decrease matrices effects. This review is an overview of current methods for thiol detection followed by the report of nanomaterial contribution to the field. Finally, a critical point of view will be given to these new sensing methods, from their potential to their limits.

1. Thiol key roles in biology and food

A thiol is a compound presenting a sulfhydryl group (SH). Thiols play a key-role in biology and also in food matrices because of their characteristic odors/taste (pleasant or unpleasant) [1,2]. In biological matrices, thiols can be divided into two different groups: low and high molecular weight thiols. The first group comprises low molecular weight thiols, one can find glutathione (GSH) and its oxidized form GSSG, cysteine (Cys) or homocysteine (Hcys) [3]. The second group comprises thiolated proteins such as albumin or hemoglobin [4]. In agri-food, low molecular weight and volatile thiols are very strong-smelling molecules that can impact the aroma of numerous foods, such as fruits, grilled meat and alcoholic [5] or non-alcoholic beverages [6]. It should also be mentioned that the simplest thiol, hydrogen sulfide (H_2S), is colorless, toxic and malodorous (rotten eggs). Characteristics and signaling of H_2S have already been discussed in many reviews dealing with this subject [7–10]. This manuscript will exclusively be focused on the other low molecular thiols.

1.1. Thiols as biomarkers

Biological fluids contain many aminothiols such as GSH, Cys and Hcys, that play a pivotal role in biological processes. GSH, a tripeptide thiol presents in most living organism cells, plays a major role as an antioxidant [11]. GSH is involved in regulating pathways, protection against radical damages [12,13], signal transduction [14], cell cycle [15] …. GSH concentrations range from 100 μM to 10 mM and from 0.6 μM to 100.0 μM in blood and plasma respectively [16]. GSH is tightly linked to GSSG and their balance gives information about the cell oxidative stress state [17] among other indications. A lot of studies took interest in investigating GSH/GSSG ratio as it will be further described [18–20]. It has been demonstrated for instance that GSH level variations are considered as a biomarker of neurodegenerative diseases (Parkinson [21], Alzheimer [22], Huntington disease [23] …).

Cys is the primary thiol-containing amino acid, synthesized in the liver from methionine [24]. It is the most abundant low molecular weight thiol in blood plasma with a physiological level comprised between 135 and 300 μM [25]. It contributes to multiple biological functions such as cell growth, lipid biosynthesis [26], skeletal muscles homeostasis [27] or in mitochondria and endoplasmic reticulum [28,29].

Hcys is an intermediate of the metabolic pathway for the conversion of methionine into Cys [30] and is present in blood plasma in a concentration ranging from 5 to 15 μM [31]. An excess of Hcys (>30 μM) is

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considered to be a risk factor for neurodegenerative (dementia [32], Alzheimer [33] …) or cardiovascular diseases [34,35].

One important biological function of both low and high molecular weight thiols is their involvement in nitric oxide (NO) storage and transportation. It is achieved through the formation of *S*-nitrosothiols (RSNO) or *S*-nitrosoproteins (PSNO) [36]. NO is a gasotransmitter involved in many physiological and pathological mechanisms [37]. RSNO allows an increase of NO half-life from few seconds to several hours, depending on the involved thiol [38–40]. Properties of RSH lead to different RSNO permeability and transport mechanisms that can influence its pharmacokinetic [41]. To increase RSNO half-life, nanotechnologies can be used to protect RSNO and control its release [42]. RSNO can be quantified through NO direct (NO probe or through its stable isotope ^{15}N [43]) and indirect (nitrite or nitrate quantification) measurements, or by thiol carrier quantification. However; when S-NO bond is broken, it leads to the formation of radical species ($RS^{\bullet}$ and $NO^{\bullet}$) with poor stability. $RS^{\bullet}$ will quickly form RSSR molecules creating a bias during identification and quantification. As an example, when it comes to GSNO quantification, nanomolar concentrations were reported in blood plasma [44–46].

1.2. Thiols as flavory compounds

In agri-food products, thiols are classified as volatile compounds and also as low molecular weight thiols contributing to aroma profile. The so-called volatile thiols are present in low concentrations in alcoholic (beer, wine…) and in non-alcoholic (coffee, fruit juices…) drinks. Thiols are actually released from their cysteinylated and gluthionylated precursors present in food matrices through alcoholic fermentation by enzymatic action of *Saccharomyces cerevisiae* [47]. When linked to these precursors, thiols are odorless (Fig. 1A) and it is only once released that they can express their full aromatic potential (Fig. 1B). Volatile thiol composition depends on yeast strain, precursor extraction from grape must and alcoholic fermentation period [48,49]. Thiols are therefore considered as key markers in the beverage quality. Their very low perception threshold (ng/L or ppt) greatly influences the taste and flavor of the product [50]. As an example, 3-mercaptohexanol (3MH) is present in wine ($0.3.10^3$ –45.10^3 nM) and fruit juice (15.10^3 –14.10^5 nM) and is responsible for grapefruit flavor. The taste of roasted coffee in the eponymous beverage but also in wine is linked to the presence of 2-furfurylthiol (2 FFT) at concentrations of approximately 250 nM in coffee and ranging from 2 to 482 nM in wine [51–53]. However, higher concentrations of 2 FFT lead to undesirable smell. Additionally, unwanted amine-like taste in beer or coffee can be linked to the presence of methylbutenethiol up to 6 nM [53,54].

Beside their organoleptic role, thiols present another function. Their antioxidant activity is linked to their stability. It has been demonstrated that low-concentrated thiols can react with Reactive Oxygen Species (ROS) to avoid oxidation and therefore drink deterioration [55–57]. On the other hand, highly-concentrated thiols lead to the generation of aldehyde species with a negative impact on drink and food taste [58]. Thiol balance needs to be maintained to ensure product quality. Three main factors influence the thiol pool: grape types [59,60], pre-fermentatives operations (vendange time, soils, grape treatment…) [61–63] and alcoholic fermentation [64–66].

1.3. Challenge

As depicted, the complete characterization of thiols in biological fluids and drinks is then crucial to predict their potential impact on health and on future customers. Therefore, there is an increasing interest in their identification and quantification.

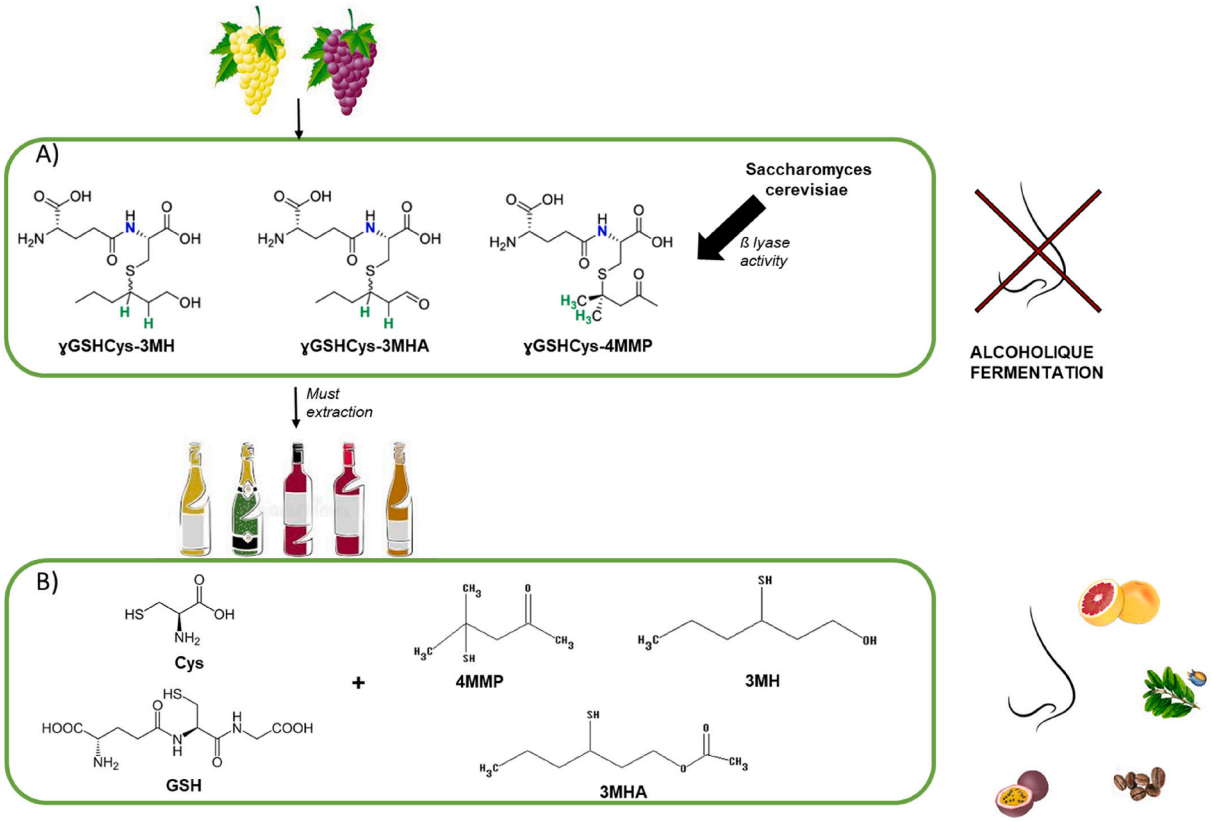

Fig. 1. Release mechanisms of thiols in wine. A) alcoholic fermentation where volatiles thiols are odorless and linked to their Cysteinylated and glutathionylated precursors. B) thiol release from their precursors associated with aromatic expression. Cys: Cysteine; Glu: Glutathione; 3MH: 3-mercaptohexanol; 3MHA: 3-mercaptohexyl acetate; 4MMP: 4-mercapto-4-methyl-2-pentanone.

For now, this section highlighted major issues concerning thiol identification and quantification: low concentrations, poor stability, high diversity and complex matrices. It genuinely addresses the issue of detection of thiolated compounds at the interface of biology and chemistry. Since few years, nanoparticles (NP) appeared as a solution in various fields of applications such as biomedical [67], environmental [68], agri-food sector [69] … Indeed, transition to the nanoscale offers new physico-chemical properties to a material such as higher specific surface area, higher reactivity… All nanomaterials developed for thiol quantification, answered traditional methods shortcomings. These approaches generally require some expensive and sophisticated apparatus (mass hyphenated systems, specific fibers…) or time-consuming analytical procedures. Moreover, these methods rely on the interactions between certain NP and thiols. It is especially true for gold nanoparticles (AuNP) having a near covalent binding energy with thiols (40–50 kcal/mol) [70]. In this paper, we aimed at providing an overview of research work employing nanomaterials for thiol sensing (identification and/or quantification), from their benefits to current methods and limits. Our review will not focus on thiol Self Assembled Monolayer, for which NP are used to nanostructure materials as it has already been extensively described in the literature [71].

2. Thiols quantification and limits

Due to thiol importance and ubiquity, analytical methods have been developed and are widely described in literature for identification and/or quantification. The quantification of these compounds remains challenging due to their reactivity (disulfide bond formation) [72], their low abundance and the complex matrices considered [49]. Different strategies have been developed to solve these issues, such as specific analytical or pretreatment methods [73–77].

For instance, pretreatment steps usually involve different types of solvents such as carcinogenic, mutagenic or reprotoxic (CMR) ones. Thiol extraction from wine often involves either dichloromethane or diethyl-ether [75,78]. These solvents are toxic, non-recyclable and must be removed before any measurements, increasing pretreatment time and manipulation steps. Pretreatments for protein removal is often required because they can interfere in chromatographic or electrophoretic analysis. In fact, proteins can affect retention time, peak shape, resolution and, of course, detection response. Three classical different approaches can be used to remove proteins: acidification, organic solvent addition and filtration [78–81]. As previously stated and depending on selected approach, process will take more time and can also be detrimental toward the molecule of interest. In blood plasma, addition of acidic agents for protein removal will decrease sample pH and favors conversion of GSH into GSNO or will lead to RSNO degradation. Furthermore, it has been demonstrated that GSH in plasma at room temperature has a half life time of approximately 20 min [82]. Thus, increasing treatment time will lead to GSH oxidation and the concentration estimated after analysis cannot reflect the initial GSH concentration. This phenomenon also occurs for food matrices because thiols are volatiles, sensitives to oxidation and very reactive [83].

Another challenge revolving in thiol quantification is the selectivity between different thiols in the same matrix. Indeed, whether in biological or food matrices, many thiols are presents. Methods should be able to allow separation of thiols or should be specific of thiols of interest. This requires pretreatment steps to isolate or select one or different thiols from their matrices. Tominaga and his team have developed an extraction method using p-hydroxymercuribenzoate sodium (pHMB) for successive liquid/liquid extraction of 3MH in wine [84]. This method was used by other researchers because of its specificity for volatile thiols against other compounds [85]. Despite its efficacy, these isolation steps increase pretreatment time and can also affect thiol concentration. To avoid these negative effects, thiol derivatization methods were developed for quantitation in an accurate and reliable way using fluorescent probes or alkylation agents [86–88]. However, these methods are complicated to develop and are not always selective toward a single thiol.

Quantification and identification methods are chosen according to the targeted concentration range. Thiols are usually present in low concentrations (down to few nanograms or nanomoles per liter). Indeed, methods should head for the lowest limits of detection (LOD). In food matrices especially, analytical methods capable of reaching such detection thresholds are required like GC coupled with mass spectrometry (MS) [89]. Analytical methods used to quantify thiols can be divided into 2 groups: non separative and separative methods. Both groups present their advantages and drawbacks that will be discussed in the following paragraphs and summarized in Table 1.

Non separative methods are simple and low cost but are affected by insufficient specificity and selectivity. Analytical methods such as UV–visible spectrophotometry, fluorimetry or amperometry are employed [90–92]. One of the first to be developed was the Ellman's Method [93]. It is a simple spectrophotometric quantification implying the reaction of thiols with 5,5′-dithiobis-(2-nitrobenzoic acid) leading to the formation of 2-nitro-5-thiobenzoate, detected at 412 nm in simple matrices (water, buffers …). This method as well as other non-separative are not selective and do not respond to thiol specificity (low concentration and complexity of matrices). Therefore, more complex methods were used to quantify and most of all separate thiols between each other to ensure a selectivity. These separative methods are more complex but they can reach picomolar LOD [73]: Liquid Chromatography (LC) or Capillary Zone Electrophoresis (CZE) allow both selectivity and sensitivity [75,94]. For example, GSH quantification in blood plasma with LC coupled with coulometric detection can achieve LOD of fM against 3 μM for a classic Ellman's method [93,95]. Because of matrices complexities, many derivative methods have also been developed [75,94].

Fig. 2 shows LOD variation as a function of the methods. Unsurprisingly, non-separative methods can be as sensitive as some separative methods but suffer from a lack of specificity. In addition, LOD are not low enough to quantify thiols with low concentrations ($<10^4$ fM). Among separative methods, fluorimetric detection appears more sensitive than UV–vis detection whether it is for LC or CZE separation. Hyphenation of MS with separation technics allows for reaching better LOD (about 10^5 times lower). For GC methods, there is no significant differences adding MS. Moreover, LOD are 10^4 times lower than LC and CZE methods. This can be explained by the fact that the GC allows to get rid of thiol complex matrices. Therefore, better thiol selectivity and sensitivity is obtained with GC and GC–MS methods. Despite this, GC methods have limitations such as equipment cost or pretreatment steps. GC methods are used for volatiles thiols and are hardly applicable to nonvolatile thiols.

According to these different aspects, analytical methods already developed present one or many disadvantages acting as obstacles to the understanding of thiol roles and mechanisms. Indeed, many methods do not allow reaching LOD in accordance with low thiols concentration [100,105,106]. More recent methods present lower LOD (<100 fM) but this high sensitivity is associated to other limitations: many pretreatments steps are required, making the method time-consuming [45,107,108]. Pretreatment also affects thiol concentrations and can require the use of harmful chemicals and/or toxic solvents [68,69,79]. Finally, several developed methods employed derivative molecules specific to SH to increase sensitivity and selectivity, while increasing sample processing time [75,94,109].

3. Nanomaterials and thiol sensing

Over the past few years, the number of publications describing the incorporation of nanomaterials in different fields has increased exponentially [110–113]. NP appears as a potential answer to some challenges previously described. Indeed, nanosystems exhibit interesting and useful properties linked to their high specific surface, reactivity, stability, catalytic activity or conductivity that can offer new

Table 1
Classical methods for thiols analysis and quantification.

Analytical Methods	Analytes	Matrices	Pretreatments	LOD (fmol/L)	Drawbacks	Ref
Spectrophotometry UV–vis	GSH	Plasma	- Masking of GSH with p-benzoquinone TNB^{2-} to remove excess of p-benzoquinone	$0.02.10^9$	Use of derivatizing agent	[95]
	GSSG	Blood	- Addition of metaphosphoric acid 20 min incubation 25 min centrifugation Complexation with Alloxan	ND	Use of derivatizing agent Enable to quantify GSSG	[94]
Fluorimetry	GSH	PBS buffer solution	- Use of DMSO Addition of p-benzoquinone for GSH selectivity	$0,1.10^9$	Not applicable to complex matrices Only applicable to GSH	[96]
	HCys		NA	$7.7.10^9$	Specific to thiol containing amino acid	[97]
LC	GSH	Grape juice and white wine	- Addition of sulfur dioxide Derivatization with p-benzoquinone	$5.5.10^7$	Use of derivatizing agent	[98]
	Cys	Plasma	- Addition of TCEP for disulfide bond reduction for 15 min Addition of PLP as derivatizing agent for 15 min at 45 °C Deproteinization with perchloric acid during 10 min	$2.5.10^9$	Time consuming Use of derivatizing agent	[99]
	HCys		- Addition of Tris(2-carboxyethyl) phosphine (TCEP) for disulfide bond reduction for 15 minAddition of pyridoxal 5′-phosphate (PLP) as derivatizing agent for 15 min at 45 °C Deproteinization with perchloric acid during 10 min	$0.25.10^9$		
	GSSG	Plasma	- Reduction of disulfide thiols Release of protein bound thiol Protein precipitation with metaphosphoric acid	5.10^3	Use of harmful chemicals Many pretreatment step	[73]
CZE	GSH	Rat Hepatocytes	- Lyses Centrifugation	$2.3.10^9$	LOD not appropriate[†]	[100]
		Saliva	- Derivatization with EMA reagent	$0.18.10^6$	Use of derivatizing agent	[101]
LC-MS	HCys	Plasma	- Reduction of disulfide bonds with Dithiothreitol (DTT) Addition of a precipitation reagent Mix for 30 min	$0.4.10^9$	Time consuming	[102]
	3MH 3MHA 4MMP 2FFT	Wine	- Addition of thiol in wine samplesDerivatization with 4,4′-Dithiopyridine (DTDP) Separation on C18 cartridge Elution with methanol Evaporation	6.10^3 1.10^4 6.10^3 6.10^3	Multiple pretreatment steps Use of harmful chemicals Derivative method	[75]
GC–MS	3MH 3MHA 4MMP 2FFT BM	Wine	- Derivatization with o-methyl hydroxylamine Separation on SPE cartridge Cartridge conditioning with dichloromethane and methanol Derivatization of retains thiolselution with solvent mixture (hexane + diethyl ether)	6.10^4 1.10^4 5.10^3 4.10^3 4.10^3	Pretreatment steps Use of harmful chemicals Time-consuming	[74]
	3MH		- Extraction in dichloromethane Liquid-liquid extraction with p-HMB Evaporation Thiol release from p-HMB with Cys Thiol extraction with dichloromethane	2.10^4	Use of harmful chemicals Multiples steps Time consuming	[89]
LC-MS/MS	GSH	Plasma	- Blocking of SH group Centrifugation Ultrafiltration	$22.5.10^6$	Multiples pretreatment steps	[45]
SPME-GC–MS	2FFT	Coffee	- Derivatization with hydroxy hydroquinone (HHQ) Dry evaporation Dissolution in water	ND	Specific only to 2FF	[103]
HS-SPME and GC–MS/MS	3MH 3MHA 4MMP	Beer	- Removing of carbon dioxide (30 min at 4 °C) Addition of triethylamine	$1.6.10^4$ $1.2.10^3$ $1.2.10^3$	Long time method development Expensive equipment	[104]

BM: Benzyl-mercaptan, CZE: Capillary Zone Electrophoresis, Cys: Cysteine, DTNB: 5,5-dithio-bis-(acide 2-nitrobenzoïque), EMA: Dimethyl sulfoxide, DMSO: Dimethyl sulfoxide,DTDP: 4,4′-Dithiopyridine DTT: Dithiothreithol, FFT: 2-Furanmethanethiol, FID: Flame Ionization Detector, FPD: Flame Photometric Detector, GC: Gas Chromatography, GSH: glutathione reduced, GSSG: Glutathione oxidized, HCl: hydrogen chloride, HHQ: hydroxy hydroquinone, HS-SPME: Head Space Solid Phase

Micro Extraction, LC: Liquid Chromatography, MS: Mass Spectrometry, NA: Non-Applicable, NaOH: sodium hydroxide, ND: non-determined, PBS: Phosphate Buffer Solution, pHMB: p-hydroxymercuribenzoate, PLP: pyridoxal 5′-phosphateSPME: Solid Phase Micro Extraction, SPE: Solid Phase Extraction, TNB^{2-}: 2-nitro-5-thiobenzoate, TCEP: Tris(2-carboxyethyl) phosphine, 3MH: 3-mercaptohexanol, 3MHA: 3-mercaptohexyl acetate, 4MMP: 4-mercapto-4-methyl-2-pentanone. When detection method is not specified, it is considered to be UV–vis detection.
†: LOD not appropriate = above thiol concentration in biomatrices (blood, plasma, saliva, urine…).

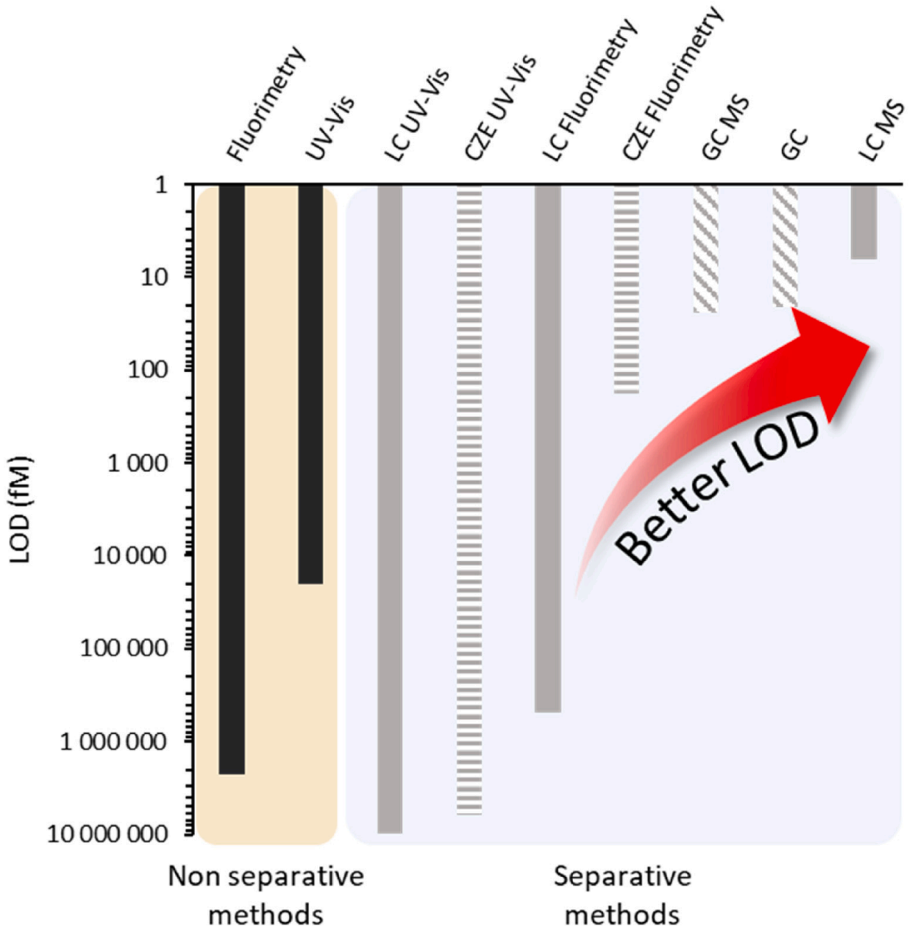

Fig. 2. LOD comparison of current thiol quantification methods (data extracted from Table 1: means of all LOD values).

functionalities to the original material [114–116] (Fig. 3). Indeed, NP with a specific affinity toward one substrate present a real interest in nanomaterial development. Before starting, the term nanomaterials will refer to colloidal NP, nanotube, nanofiber… While nanostructurated materials will described materials with new abilities granted by the addition of nanomaterials. Nanomaterials have been at the forefront of research for thiol quantification.

NP can act as sensors to detect thiol traces through specific interactions, allowing capture, purification or pre-concentration of a thiol from a sample. Considering that thiols are present at low concentrations, nanomaterials can be used to directly quantify these molecules or as a pretreatment step for extraction, enrichment or purification from their matrices. The most described in literature are gold nanomaterials [117] due to their strong affinity for SH function (binding energy around 40–50 kcal/mol) [70]. NP characteristics (size, shape, composition …) play a key role in their analytical capacity. For instance, NP shape and size will influence the number of available sites for thiol bounding. Table 2 summarizes, in a non-exhaustive way, nanosensing thiol methods developed over the past 10 years.

3.1. Optical methods

3.1.1. Colorimetric sensing

Based on optical properties of NP, and more specifically the presence of surface-plasmon resonance characteristic of metallic NP, different colorimetric assays have been developed to detect and quantify thiols. These methods are easy to develop, rapid and low cost.

Thiol colorimetric detection methods are mostly based on AuNP aggregation and/or resonance plasmon band modification. Colorimetric methods have been developed and published, based on AuNP aggregation [118,120,121]. He *et al.* has developed a colorimetric detection method for GSH and Cys [119]. It is based on chronometric method of blue methylene and hydrazine catalyzed by AuNP. In absence of the two thiols, the blue solution becomes colorless due to the presence of AuNP in 10 min. The presence of thiol, that are known to show high affinity for AuNP, inhibits their catalytic activity, increasing the reaction time up to several hours. It is directly related to GSH or Cys concentration [119]. The selectivity of this method for the two thiols compared to other amino acid was investigated and showed non-significative changes of reaction time.

Although AuNP are the most described nanomaterials, other compositions have been developed. Ju and his team synthesized silver NP (AgNP) on nitrogen-doped graphene quantum dots (*N*-GQD). In

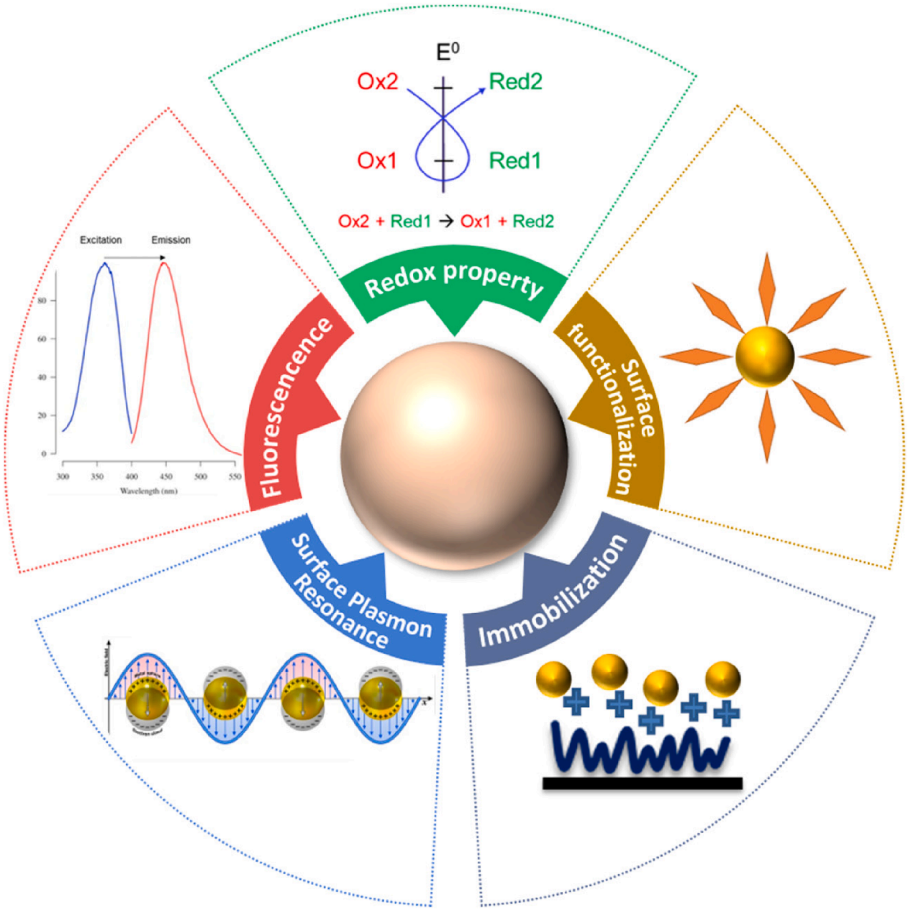

Fig. 3. NP properties for thiol detection methods.

presence of tetramethylbenzidine (TMB) and H_2O_2, oxidation of TMB in oxTMB occurs. This oxidation resulted in 2 absorption peaks at 652 and 890 nm. Adding GSH to this previous solution, reduction of oxTMB in TMB resulted in decrease of adsorption peak at 652 nm which is dependent on GSH concentration. Absorbance monitoring at 652 nm allows to quantify GSH concentration in blood plasma with a LOD of 31.10^6 fM [135]. In the same way, Zhou *et al.* developed a thiol sensing method using silver nanoprism based on wavelength displacement after thiol adsorption on silver [152]. This method allows GSH, Cys and dithiothreitol (DTT) selectivity in serum with a LOD of 10.10^6 fM.

Even if they present good selectivity and sensitivity, these methods used colloidal NP with stability issues [164]. Furthermore, physicochemical properties greatly influence thiol interaction and detection. Thus, a routine use of these methods requires a rigorous knowledge and control of NP characteristics which is restrictive for industrial production [165]. Finally, NP aggregation makes the probe non-reusable.

3.1.2. *Fluorescence-based sensing*

Most of nanomaterials for fluorimetric thiol sensing are based on fluorescence quenching which refers to the process by which fluorescence intensity of a sample decreases or increases (Fig. 4). This deactivation/activation mechanism is caused by molecular interaction [154]. The changes in fluorescence intensity can be used as source of information for some biological systems (like quencher accessibility to fluorophore or quencher/fluorophore quantity).

Metallic nanomaterials (AuNP, AgNP …) show interesting optical properties and high fluorescence quenching efficiency [167], which are affected by NP size and geometry. Combination of chromophores and metallic NP can therefore serve as sensor. The strong bond between AuNP and -SH groups allows a preferential adsorption with a desorption of a chromophore presenting lower affinity. Among the different fluorescent ligand, Nile Red (NR) is one of the most described in literature. However, Kapur *et al.* synthesized protein functionalized AuNP using mCherry protein which is quenched when bound to AuNP. These NP targeted thiols are based on the competitive displacement of mCherry for adsorption of thiols. It resulted in an increasing fluorescence due to mCherry release in the medium, correlated with the quantity of adsorbed thiols. They also showed that kinetics and thiol types played a key-role in chemical adsorption on AuNP, and therefore on the observed fluorescence [136]. Other nanoparticles-based methods were developed using different ligands. Luo and his team designed a nanoprobe composed of AuNP functionalized with a Redox responsive Silica (ReSi) matrix linked with Fluorescein IsoThioCyanate (FITC). In presence of GSH (or other thiols) at relatively high concentrations (10 mM), a destruction of the disulfide-linked ReSi-FITC resulted in the release of FITC and recovery of native fluorescence of the free-probe [137]. Based on the same mechanism, Xu and co-workers designed an AuNP sensor functionalized with BODIPY (fluorescent molecule) quenched by the presence of Cys or GSH in living cells. The signal response was thiol specific, fast and with a LOD of 30.10^6 fM [139]. Other identical methods are described in literature with LOD of nanomolar level [134,138,140,142,168].

Even though AuNP are more widely described, researchers have developed similar method based on fluorescence properties of other NP. Zhang *et al.* who used turn-off fluorescence-based method with AuNP and Silicon NP (SiNP) [148]. Addition of Cys led to a release of AuNP adsorbed from SiNP surface and restored the fluorescence. LOD was estimated at 35.10^9 fM in ethanolic solution. AgNP was also widely used as for example by Li and his team who developed Silver nanocluster (AgNC) stabilized by single-stranded DNAs (DNA-AgNC). In presence of

Table 2
Nanomaterial based methods for thiols analysis and quantification.

NP			Analytes	matrices	Mechanisms	Analytical methods	LOD (fmol/L)	Drawbacks	REF
Core	**Ligand**	**Size (nm)**							
AuNC	polyvinylpyrrolidone (PVP)	9 (D_h)	Cys GSH HCys	PBS	Competitive displacement	Fluorimetry	35.10^6	ND	[118]
AuNP	Citrate	13 (D_h)	Cys GSH	Fetal bovine serum	Reaction between methylene blue and hydrazine catalyzed by AuNP. Reaction time decreased when thiol interact with AuNP.	Spectrophotometry	10.10^9 8.10^9	Reaction time: 2 h30 with GSH LOD not appropriate Non-reusable	[119]
		ND	GSH	Water	Detect oxidative stress. GSH generate AuNP aggregation with APTES and not GSSG.		ND	Non-reusable	[120]
		8 (D_c)	Thiourea	Waste water	Aggregation of AuNP and wavelength displacement		$2.14.10^6$	Non-reusable	[121]
		10.8 (D_h)	Cys	Water	Aggregation of AuNP and wavelength displacement		10.10^3	Selectivity with other thiols Non-reusable	[122]
		13 (D_h)	Cys	Water	Aggregation of AuNP and wavelength displacement		100.10^6	Selectivity with other thiols Non-reusable	[123]
		ND	GSH GSSG	Cells	Thiol selective probe on nanoporous silicon chip	SALDI-MS	3.10^9	GSSG detection need reduction step	[124]
		13 (D_h)	GSH	Liver	Thiol selective probe	MALDI-TOF-MS	2.10^9	ND	[125]
		20 (D_h)	GSH	Saliva urine	AuNP immobilized on syringe to act as solid-phase extraction followed by DTT desorption	LC	5.10^6	Loss or desorption of AuNP not evaluated	[126]
		6 (D_h)	GSH NAC	PBS Plasma	Immobilization onto a cellulosic membrane to selectively capture thiol	LC	$0.5.10^9$	Non-recyclable	[127]
		16 (D_h)	GSNO	Plasma	Indirect GSNO quantification by denitrosation	Amperometric	100.10^6	Non-reusable Blocking step for other free thiols	[128]
		10–20 (D_h)	GSH	Skin	Immobilization of AuNP on a paper for thiol sensing by color change of paper due to AuNP aggregation	Visual	$6.9.10^9$	Analysis based on photography	[129]
	Tween-20	13 (D_c)	GSH	Seawater	Selective thiol enrichment with AuNP followed by DTT desorption and CZE analysis	CZE	2.10^6	Selectivity with other thiols not tested	[130]
		13 (D_c)	Cys GSH Hcys	Plasma	Selective thiol enrichment with AuNP followed by DTT desorption and CZE analysis		10.10^6 –65.10^6	Non-reusable	[131]
		13 (D_c)	Cys GSH Hcys	Buffer	Selective thiol enrichment with AuNP followed by DTT desorption and CZE analysis		554.10^6 28.10^6 456.10^6	Insufficient extraction due to AuNP or DTT low concentration	[132]
		ND		Saliva			5.10^6	Non-reusable	[133]

(*continued on next page*)

Table 2 (*continued*)

NP			Analytes	matrices	Mechanisms	Analytical methods	LOD (fmol/L)	Drawbacks	REF
Core	**Ligand**	**Size (nm)**							
			Cys GSH Hcys Methionine		Selective thiol enrichment with AuNP followed by DTT desorption and CZE analysis				
	Rhodamine G	20 (D_h)	Cys GSH	Buffer	Reduced thiols were blocked with *N*-ethylmaleimide and oxidized thiols was quantified by competitive displacement	Fluorimetry	$0.57.10^9$ $0.68.10^9$	Pretreatment needed Non-reusable	[134]
	ND	19 (D_c)	GSH	water	AgNP catalyzes oxidation of TMB with H_2O_2 and GSH reduced oxTMB (color change)	Spectrophotometry	31.10^6	Non-reusable	[135]
	mcherry	13 (D_c)	Cys GSH	Buffer	Competitive displacement of mcherry (thiol dependent)	Fluorimetry	ND	Non-reusable	[136]
	Silica + fluorescein isothiocyanate	10 (D_c)	GSH	Cells	Release of fluorescein by GSH		ND	Non-reusable Selectivity not tested	[137]
	$NaYF_4:Yb^{3+},Er^{3+}$	40 (D_h)	GSH	Buffer	Competitive displacement		30.10^6	Non-reusable Selectivity not tested	[138]
	BODIPY	15 (D_h)	Cys Hcys	Cells	Competitive displacement		ND	Non-reusable	[139]
	Patterned poly(acrylic acid)	25 (D_c)	GSH	Buffer	Thiol selective probe	SALDI-MS	$0.1.10^6$	Not thiol selective Non-reusable	[140]
	Citrate cetyltrimethylammonium bromide Sodium borohydride	20 152.5 (D_c)	GSH Cys GSSG	plasma	Aggregation of AuNP and wavelength displacement	Spectrophotometry	$1.5.10^{12}$ - 1.10^9	Non-reusable	[141]
	Chitosan	ND	Cys	Water	Aggregation of AuNP and wavelength displacement		$0.1.10^9$	Non-reusable	[142]
AuNP AgNP	ND	10–20 (D_c)	GSH	Cells	Thiol selective probe	SALDI-MS	ND	Selectivity with other thiols not tested Non-applicable to GSSG quantification	[143]
AuNP Carbon QD	citrate	3.74.7 (D_c)	Cys	milk	Competitive displacement	Fluorimetry	12.10^6	Selectivity not tested Non-reusable	[144]
AuNC SiQD	ND	ND	Cys		Competitive displacement	Fluorimetry	10.10^6	Selectivity not tested Long NP synthesis process	[145]
Nanoporous Gold	ND	ND	Dodecanethiol	Ethanol	solid-phase microextraction	GC–MS	$0.1.10^9$	Use of harmful chemicals	[146]
Nanoporous Gold	ND	ND	Alkanethiol	Ethanol	solid-phase microextraction		ND	Use of harmful chemicals	[147]
Silicon NP	AuNP	40 (D_h)	Cys	Buffer	Competitive displacement	Fluorimetry	35.10^9	Non-reusable Selectivity not tested	[148]
AgNP	DTNB	20–60 (D_h)	GSH DTNB	PBS	Immobilization onto a porous silicon disk for surface-enhanced Raman scattering application	Raman Spectroscopy	$74.9.10^6$ 10.10^6	Selectivity tested with Cys and HCys only	[149]
AgNC	DNA	7 (D_c)	Cys GSH	Water	Competitive displacement	Fluorimetry	$0.45.10^9$ $4.50.10^9$	Non-reusable	[150]

(*continued on next page*)

Table 2 (*continued*)

NP			Analytes	matrices	Mechanisms	Analytical methods	LOD (fmol/L)	Drawbacks	REF
Core	**Ligand**	**Size (nm)**							
	sodium dodecyl sulfate	ND	Cys		Aggregation of AuNP and wavelength displacement		83.10^6	Selectivity with other thiols not tested Non-reusable	[151]
Silver nanoprism	Citrate	30 (D_c)	Cys GSH dimercaptosuccinic acid mercaptopropionic acid DTT	serum	Wavelength displacement	Spectrophotometry	10.10^6	Non-reusable	[152]
Graphene QD	ND	2 (D_h)	Cys GSH Hcys	serum	Competitive displacement	Fluorimetry	$2.5.10^6$ $5.0.10^6$ $5.0.10^6$	Non-reusable Interferences with amino acids	[153]
Carbon dots	ND	2 (D_c)	Cys GSH Hcys	Buffer	Competitive displacement		69.10^6 80.10^6 76.10^6	Non-reusable	[154]
	Rhodamine B	2–3 (D_c)	GSH	Water Plasma food	Competitive displacement		20.10^6	Non-reusable Selectivity with other thiols not tested	[155]
	Metal ions	16 (D_c)	2-mercaptoethanol mercaptoacetic acid	fetal bovine serum	Competitive displacement		1.10^9	Non-reusable Selectivity with other thiols not tested LOD not appropriate	[156]
	Au	7 (D_c)	6-Thioguanine	NA	Competitive displacement		$10.\ 10^6$	Non-reusable Selectivity with other thiols not tested	[157]
nitrogen-doped graphene QD	ND	2.2 (D_c)	Cys GSH	Water	Competitive displacement		36.10^6 34.10^6	Non-reusable	[158]
	ND	3–5 (D_c)	GSH	PBS	Competitive displacement		$30.\ 10^6$	Non-reusable Selectivity with other thiols not tested	[159]
	ND	10(D_h)	Cys GSH	PBS	cobalt phthalocyanine immobilized on nitrogen-doped graphene QD onto a glassy carbon electrode showed electrocatalytic activity towards the oxidation of three different thiols	Amperometry	1.10^9	LOD not appropriate	[160]
nitrogen-doped graphene QD + V_2O_5 nanosheets	ND	2–8 (D_c)	Cys	Serum	Competitive displacement	Fluorimetry	50.10^6	Non-reusable Selectivity with other thiols not tested	[161]
ZnO NR	AuNP	4.32 (D_c)	GSH	Water	Thiol selective probe with ZnO NR desorption improvement	SALDI-MS	150.10^{-3}	ND	[162]
AuNP Pt NS Fe_3O_4 NP TiO_2 NP Se NP CdTe QD	ND	14 37 13 5 100 3	GSH	Water	Thiol selective probe		$1.4.10^2$ $2.3.10^4$ $8.3.10^3$ $2.2.10^3$ $3.3.10^4$ $1.9.10^2$	Desorption problems for Pt NS	[163]

APTES: 3-Aminopropyltriethoxysilane, AgNC: Silver Nanocluster, AgNP: Silver Nanoparticles, CdSe: Cadmium selenide, CdTe: Cadmium telluride, Cys: Cysteine, CZE: Capillary Zone Electrophoresis, Dc = core diameter, Dh = Hydrodynamic Diameter, DNA: Deoxyribonucleic Acid, DTNB: 5,5-dithio-bis-(acide 2-nitrobenzoïque), DTT: Dithiothreitol, GC: Gas Chromatography, GSH: Glutathione reduced, GSNO: *S*-nitrosoglutathione, GSSG: Glutathione oxidized, Hcys: Homocysteine LC: Liquid Chromatography, LOD: Limit Of Detection, MALDI-MS: Matrix Assisted Laser Desorption Ionization, MALDI-TOF-MS: Matrix Assisted Laser Desorption Ionization - Time of Flight – Mass Spectrometry, MS: Mass Spectrometry, NAC: *N*-Acetylcysteine, ND: non-determined, NP: Nanoparticles, NR: NanoRod, NS: NanoSponge, NT: NanoTube, OxTMB: 3,3′,5,5′-Tetramethylbenzidine oxidized, PVP: polyvinylpyrrolidone, QD: Quantum Dots, SALDI-MS: Surface-Assisted Laser Desorption/Ionization- Mass Spectrometry, TGA: Thioglycolic Acid, TMB: 3,3′,5,5′-Tetramethylbenzidine, ZnO: Zinc Oxide.
When detection method is not specified, it is considered to be UV–vis detection.
† : LOD not appropriate = above thiol concentration in biomatrices (blood, plasma, saliva, urine…).

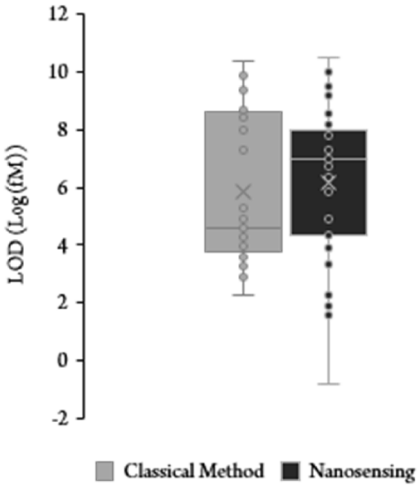

Fig. 4. Direct LOD comparison between classical methods (grey box) and nanosensing methods (black box) (Data extracted from Tables 1 and 2).

GSH or Cys, an adsorption on AgNC occurred, leading to formation of a nonfluorescent complex and/or aggregation of AgNC, decreasing fluorescence intensity. LOD were reported to $0.134.10^9$ fM and $0.172.10^9$ fM for GSH and Cys, respectively [150]. Wu *et al.* developed a fluorescent probe using graphene QD (GQDs) which emitted strong blue fluorescence in aqueous buffer solution, quenched in presence of mercury (II) ions. In presence of GSH, Cys and Hcys, Hg^{2+} release occurred and a fluorescence turned on, directly correlated to thiol concentration. The assay was highly sensitive with LOD of $5.0.10^6$, $2.5.10^6$ and $5.0.10^6$ fM for GSH, Cys and Hcys, respectively. However, some interferences with amino acids and proteins were observed [153]. Many similar methods were developed using carbon dots (CD) [155–157,159] or nitrogen-doped graphene QD [158,161].

Nanoparticle fluorescence-based methods have been extensively used for rapid thiol detection, however they present few limitations. In the same way as colorimetric assays, these methods are linked to NP stability and are for single-use.

3.2. Other non-separative methods

The main goal of using NP-based materials is thiol amplification/ separation/ extraction from their matrices for chemical and biological detection. Recently, NP have been widely employed for determination of thiol analysis in Matrix Assisted Laser Desorption/Ionization Mass Spectrometry (MALDI-MS) and SALDI-MS. The use of NP presents two interests: the first is energy absorption of laser and its transfer that will induce desorption and ionization of the analyte with a high efficiency. The second advantage is the specific interaction between NP and the analyte, acting as a selective probe. Most of studies report the use of AuNP [124,125,140,143,162] because of their strong affinity for thiols but other NP can be used. That is why Chiang *et al.* investigated six different types of colloidal NP for GSH quantification in SALDI-MS. This paper is older than 10 years but presented for the first-time interesting comparisons between different nanomaterials in terms of thiol sensing: AuNP, TiO_2 NP, Se NP, CdTe QD, Fe_3O_4 NP and Pt Nanosponges (Pt NS). Previously mentioned NP employed reached LOD of femtomolar level. The sensitivity of Pt NS for SALDI-MS appeared to be less important than other NP because of too strong interaction with the analyte. Pt-S bound energy is 50 kcal/mol [169] which is too strong to efficiently desorb GSH and explained the high values of the obtained variation coefficients.

Concerning RSNO compounds, nanomaterials are useful for denitrosation (from RSNO to $RS^{\bullet}$ + $^{\bullet}NO$). Baldim *et al.* developed an analytical method based on the use of AuNP for the decomposition of RSNO. The NO release is monitored by amperometry and can be directly related to the initial RSNO concentration. They also studied GSNO saturation of the colloidal AuNP suspension by successive additions of GSNO. They showed that a saturated state was achieved with 30 μM of GSNO for 9 nM AuNP suspension. Considering the specific interaction between other blood plasma thiols and AuNP, authors decided to block SH function with iodoacetic acid. Thus, only RSNO can interact with AuNP. They determined the blood plasma volume saturating an AuNP suspension and the effect of other RSNO present in plasma amperometric signal, steric hindrance caused by albumin for example [128]. This method employed an indirect quantification of RSNO through NO quantification. However, NO have a very short half-life (few seconds) which may lead to underestimation of RSNO concentration.

3.3. Separative methods

Separative methods can be associated to nanomaterials to increase selectivity and sensitivity for thiols. Shen *et al.* developed a method using CZE coupled to Tween 20 capped AuNP [130]. The first step is the extraction of thiols from the matrix (seawater). The use of Tween 20 as a ligand allows AuNP dispersion in highly saline solution. After a release of adsorbed molecules by ligand exchange with DTT, desorbed thiols were derivated with *o*-phtalaldehyde (OPA), resulting in the formation of isoindole. Authors proved that their process is able to separate five thiols with LOD down to $0.1.10^3$ –$6.0.10^3$ fM. Drawback of this method is the possible interaction with amino containing molecule because OPA is not thiol specific. It is a reagent normally used for amine quantification. Method without derivatization using also Tween 20-capped AuNP was developed by Wang *et al.* [133]. Thiols were adsorbed on NP (60 min) followed by a release step and a CZE quantification. 3 different releasing agents, commonly used were tested (DTT, 2,3-Dimercapto-1-propanol and 2-mercaptoethanol). The lower LOD was obtained for GSH (5.10^6 fM) with a 2-mercaptoethanol release. Literature report other AuNP nanomaterials coupled to CZE method [130,131,133]. These methods employed Tween 20-capped AuNP for GSH extraction and desorption (through DTT ligand exchange) with the highest LOD being 2.10^6 fM.

Less described, nanostructurated devices allowed to get rid of stability issues and pretreatment step (in previously described methods) such as centrifugation to remove colloidal NP. Researchers created an AuNP-coated syringe for GSH extraction from biological matrices followed by a release step using DTT and a LC quantification [126]. Syringes were coated using layer-by-layer method and allowed to reach a LOD of 5.10^6 fM for GSH in saliva. Nanostructurated materials coupled with separative methods were also described for alkanethiol quantification. GC–MS methods were developed with Solid Phase Micro

Extraction (SPME) fibers coated with AuNP to capture thiols compounds while being thermally desorbed in GC headspace. Efficiency of SPME coated fibers appeared to be 11 times higher than non-coated fibers in term of sensitivity [146]. This method was able to selectively analyze and quantify mixture of alkanethiols (hexanethiol, octanethiol, and dodecanethiol) with higher extraction efficiency than a classical GC–MS headspace analysis but requiring higher desorption energy [147]. In the same way, a syringe filter cellulosic membrane has been developed in our lab, with AuNP adsorbed through electrostatic interactions with a positively charged polymer previously immobilized on the substrate [127]. Thiols (either in simple or complex matrices) were adsorbed by filtration without any pretreatment of the sample and released by chemical desorption (ligand exchange) before HPLC analysis. The coated filter was able to adsorb NAC and GSH quantities up to 270 and 70 nmol respectively. Thiol specificity and concentrating power have been demonstrated and results suggest the possibility to apply the device on any type of biological or food matrices. A similar strategy was also developed by Mompó-Roselló *et al,* through the direct coating of a syringe core. However, we observed that AuNP attached to plastic walls are removed with each piston passage, suggesting that immobilization developed by Mompó-Roselló *et al.* may be unstable against strong shear stresses. Among nanostructurated devices developed, literature described AuNP immobilization on a glass microfluidic channel surface in electrophoresis (fluorescent mode) microchips for GSH quantification in bacteria (*E. coli*, *S. aureus* and *S. enterica)* with $0.01.10^6$ fM LOD [132]. AuNP Nanostructurated papers were developed by Markina and his team to visually evaluate presence of thiol in human skin [129]. The detection procedure implied the assessment of the color change of the paper sensor resulting from aggregation of gold nanoparticles caused by thiols with $6.9.10^9$ fM LOD.

Separative methods using nanomaterials present better selectivity and specificity than optical methods. However, strong interactions between NP and thiols lead to desorption issues for SALDI/MALDI-MS methods. Furthermore, to increase thiol selectivity, many methods use derivatizing agent implying an increase in pretreatment time. Finally, promising results were obtained with nanostructurated materials as sample pretreatment support, avoiding stability and pretreatment issues.

4. Conclusion

This review offers an overview of thiol analysis issues, intrinsically linked to their properties and characteristics. Most of current methodologies present a lack of sensitivity, or require many pretreatment steps to overcome these drawbacks. In that way, analytical methods based on nanomaterials were developed. The overwhelming majority employed metallic nanoparticles, with more than 73 % being constituted of Au according to our reading (Table 2). New methods were developed, based on aggregation, coupling, fluorescence enhancement, fluorescence quenching, resonance light scattering and so on. Those reach nanomolar LOD and restrict the need for pretreatment steps since AuNP share specific interactions with thiols. Considering the literature, we noticed that LOD depends on NP size and type but also on ligand nature when functionalized. However, as most of them are based on fluorimetric or colorimetric detection without hyphenation to separative methods, thiol discrimination remains a challenging step. Moreover, some of these methods are unsuitable for routine use in a laboratory due to several issues: non-recyclability of nanomaterial, poor colloidal stability of NP (long term storage, pH sensitivity…) or handling complexity. There is therefore a compromise between an affordable method without selectivity (metallic NP and UV–vis detection for example) and an expensive equipment or nanomaterials harder to develop for routine use but reaching expected sensitivity and selectivity. When it comes to LOD, some nanosensing methods are able to reach values of a few femtomolar, even if median LOD appear to be similar as classical methods (Fig. 4).

Finally, few methods using nanostructurated materials (immobilized NP, nanosized pores … [146,147,171]) were developed and appeared promising. Their principal advantages lie in easy handling, potential reuse and an absence of colloidal instability or interferences from matrices. Those devices still require further development steps with strict NP control (monodispersed sizes, controlled charges, homogenous functionalization…) and device characterization (immobilization density, fabrication reproducibility, stability…).

Whether it is for nanomaterial or nanostructurated material, disadvantages were highlighted: the lack of stability of colloidal nanoparticles and the impossibility to obtain a reusable method for thiol sensing. Indeed, phenomena on which detection and/or separation are based lead to nanoparticles and/or sensor destruction. In the next few years, main challenge will remain in the development of a nanostructurated device, such as a kit, for fast, sensitive and specific thiol sensing in different matrices. It should have the following characteristics: high density of immobilized NP, applicable to different media (pH, salt concentration, complexity …) with the possibility of hyphenation to several analytical methods. Finally, the reusability would be an asset in terms of green chemistry and/or ecology.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

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

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References

[1] B. Quintanilla-Casas, N. Dulsat-Serra, N. Cortés-Francisco, J. Caixach, S. Vichi, Thiols in brewed coffee: assessment by fast derivatization and liquid chromatography–high resolution mass spectrometry, LWT – Food Sci. Technol. 64 (2015) 1085–1090, https://doi.org/10.1016/j.lwt.2015.07.010.
[2] N. Müller, D. Rauhut, Recent developments on the origin and nature of reductive sulfurous off-odours in wine, Fermentation 4 (2018) 62, https://doi.org/10.3390/fermentation4030062.
[3] K. Van Laer, C.J. Hamilton, J. Messens, Low-molecular-weight thiols in thiol-disulfide exchange, Antioxid. Redox Signal. 18 (2013) 1642–1653, https://doi.org/10.1089/ars.2012.4964.
[4] O. Rudyk, P. Eaton, Biochemical methods for monitoring protein thiol redox states in biological systems, Redox Biol. 2 (2014) 803–813, https://doi.org/10.1016/j.redox.2014.06.005.
[5] A. Roland, R. Schneider, A. Razungles, F. Cavelier, Varietal thiols in wine: discovery, analysis and applications, Chem. Rev. 111 (2011) 7355–7376, https://doi.org/10.1021/cr100205b.
[6] R.J. Cannon, C.-T. Ho, Volatile sulfur compounds in tropical fruits, J. Food Drug Anal. 26 (2018) 445–468, https://doi.org/10.1016/j.jfda.2018.01.014.
[7] B. Olas, Hydrogen sulfide in signaling pathways, Clin. Chim. Acta 439 (2015) 212–218, https://doi.org/10.1016/j.cca.2014.10.037.
[8] E. Zaorska, L. Tomasova, D. Koszelewski, R. Ostaszewski, M. Ufnal, Hydrogen sulfide in pharmacotherapy beyond the hydrogen sulfide-donors, Biomolecules 10 (2020) 323, https://doi.org/10.3390/biom10020323.
[9] B.D. Paul, S.H. Snyder, Gasotransmitter hydrogen sulfide signaling in neuronal health and disease, Biochem. Pharmacol. 149 (2018) 101–109, https://doi.org/10.1016/j.bcp.2017.11.019.
[10] M. Bhatia, Hydrogen sulfide as a vasodilator, IUBMB Life 57 (2005) 603–606, https://doi.org/10.1080/15216540500217875.
[11] C. Gaucher, A. Boudier, J. Bonetti, I. Clarot, P. Leroy, M. Parent, Glutathione: antioxidant properties dedicated to nanotechnologies, Antioxidants 7 (2018) 62, https://doi.org/10.3390/antiox7050062.
[12] K. Helbig, C. Bleuel, G.J. Krauss, D.H. Nies, Glutathione and transition-metal homeostasis in Escherichia coli, J. Bacteriol. 190 (2008) 5431–5438, https://doi.org/10.1128/JB.00271-08.
[13] S. Srivastava, K.V. Ramana, A. Bhatnagar, S.K. Srivastava, Synthesis, quantification, characterization, and signaling properties of glutathionyl

conjugates of enals, Methods Enzymol. 474 (2010) 297–313, https://doi.org/10.1016/S0076-6879(10)74018-0.
[14] R. Janaky, K. Ogita, B.A. Pasqualotto, J.S. Bains, S.S. Oja, Y. Yoneda, C.A. Shaw, Glutathione and signal transduction in the mammalian CNS, J. Neurochem. 73 (1999) 889–902, https://doi.org/10.1046/j.1471-4159.1999.0730889.x.
[15] P. Diaz-Vivancos, A. de Simone, G. Kiddie, C.H. Foyer, Glutathione – linking cell proliferation to oxidative stress, Free Radic. Biol. Med. 89 (2015) 1154–1164, https://doi.org/10.1016/j.freeradbiomed.2015.09.023.
[16] A. Meister, On the discovery of glutathione, Trends Biochem. Sci. 13 (1988) 185–188, https://doi.org/10.1016/0968-0004(88)90148-x.
[17] L. Flohe, The fairytale of the GSSG/GSH redox potential, Biochim. Biophys. Acta-Gen. Subj. 2013 (1830) 3139–3142, https://doi.org/10.1016/j.bbagen.2012.10.020.
[18] L. Cao, D. Waldon, Y. Teffera, J. Roberts, M. Wells, M. Langley, Z. Zhao, Ratios of biliary glutathione disulfide (GSSG) to glutathione (GSH): a potential index to screen drug-induced hepatic oxidative stress in rats and mice, Anal. Bioanal. Chem. 405 (2013) 2635–2642, https://doi.org/10.1007/s00216-012-6661-8.
[19] C. Romagnoli, G. Marcucci, F. Favilli, R. Zonefrati, C. Mavilia, G. Galli, A. Tanini, T. Iantomasi, M.L. Brandi, M.T. Vincenzini, Role of GSH/GSSG redox couple in osteogenic activity and osteoclastogenic markers of human osteoblast-like SaOS-2 cells, Febs J. 280 (2013) 867–879, https://doi.org/10.1111/febs.12075.
[20] E. Nur, M. Verwijs, D.R. de Waart, J.-J.-B. Schnog, H.-M. Otten, D.P. Brandjes, B. J. Biemond, R.P.J.O. Elferink, Increased efflux of oxidized glutathione (GSSG) causes glutathione depletion and potentially diminishes antioxidant defense in sickle erythrocytes, Biochim. Biophys. Acta-Mol. Basis Dis. 2011 (1812) 1412–1417, https://doi.org/10.1016/j.bbadis.2011.04.011.
[21] G.D. Zeevalk, L. Manzino, P.K. Sonsalla, L.P. Bernard, Characterization of intracellular elevation of glutathione (GSH) with glutathione monoethyl ester and GSH in brain and neuronal cultures: Relevance to Parkinson's disease, Exp. Neurol. 203 (2007) 512–520, https://doi.org/10.1016/j.expneurol.2006.09.004.
[22] S. Charisis, E. Ntanasi, M. Yannakoulia, C.A. Anastasiou, M.H. Kosmidis, E. Dardiotis, G. Hadjigeorgiou, P. Sakka, A.S. Veskoukis, D. Kouretas, N. Scarmeas, Plasma GSH levels and Alzheimer's disease. A prospective approach: results from the HELIAD study, Free Radic. Biol. Med. 162 (2021) 274–282, https://doi.org/10.1016/j.freeradbiomed.2020.10.027.
[23] J. Sian, D.T. Dexter, A.J. Lees, S. Daniel, Y. Agid, F. Javoy-Agid, P. Jenner, C. D. Marsden, Alterations in glutathione levels in Parkinson's disease and other neurodegenerative disorders affecting basal ganglia, Ann. Neurol. 36 (1994) 348–355, https://doi.org/10.1002/ana.410360305.
[24] M. Wirtz, M. Droux, Synthesis of the sulfur amino acids: cysteine and methionine, Photosynth. Res. 86 (2005) 345–362, https://doi.org/10.1007/s11120-005-8810-9.
[25] R.M. Strongin, Selective Indicators for Optical Determination of Disease Biomarkers - ProQuest, Chemistry, Portland State University, 2014. https://search.proquest.com/openview/76628d003462672f310f334d1420887e/1?pq-origsite=gscholar&cbl=18750&diss=y.
[26] J. Yin, W. Ren, G. Yang, J. Duan, X. Huang, R. Fang, C. Li, T. Li, Y. Yin, Y. Hou, S. W. Kim, G. Wu, L-Cysteine metabolism and its nutritional implications, Mol. Nutr. Food Res. 60 (2016) 134–146, https://doi.org/10.1002/mnfr.201500031.
[27] I. Papet, D. Rémond, D. Dardevet, L. Mosoni, S. Polakof, M.-A. Peyron, I. Savary-Auzeloux, Sulfur Amino Acids and Skeletal Muscle, in: 2019: pp. 315–343. 10.1016/B978-0-12-810422-4.00020-8.
[28] S. Shahrokhian, Lead phthalocyanine as a selective carrier for preparation of a cysteine-selective electrode, Anal. Chem. 73 (2001) 5972–5978, https://doi.org/10.1021/ac010541m.
[29] D.W. Bak, T.J. Bechtel, J.A. Falco, E. Weerapana, Cysteine reactivity across the subcellular universe, Curr. Opin. Chem. Biol. 48 (2019) 96–105, https://doi.org/10.1016/j.cbpa.2018.11.002.
[30] E. Lonn, Homocysteine lowering with folic acid and b vitamins in vascular disease, N. Engl. J. Med. 354 (2006) 1567–1577, https://doi.org/10.1056/NEJMoa060900.
[31] M.A. Mansoor, A.M. Svardal, P.M. Ueland, Determination of the in vivo redox status of cysteine, cysteinylglycine, homocysteine, and glutathione in human plasma, Anal. Biochem. 200 (1992) 218–229, https://doi.org/10.1016/0003-2697(92)90456-h.
[32] J. Sławek, M. Białecka, Chapter 57 - Homocysteine and Dementia, in: C.R. Martin, V.R. Preedy (Eds.), Diet Nutr. Dement. Cogn. Decline, Academic Press, San Diego, 2015: pp. 611–621. 10.1016/B978-0-12-407824-6.00057-4.
[33] K. Miwa, M. Tanaka, S. Okazaki, Y. Yagita, M. Sakaguchi, H. Mochizuki, K. Kitagawa, Increased total homocysteine levels predict the risk of incident dementia independent of cerebral small-vessel diseases and vascular risk factors, J. Alzheimers Dis. JAD. 49 (2016) 503–513, https://doi.org/10.3233/JAD-150458.
[34] I. Graham, E. Leslie, L.E. Daly, H. Refsum, K. Robinson, L.E. Brattström, P. M. Ueland, R.J. Palma-Reis, G.H.J. Boers, R.G. Sheahan, B. Israelsson, S. Cuna, C. S. Uiterwaal, R. Meleady, D. McMaster, P. Verhoef, J. Witteman, P. Rubba, H. Bellet, J.C. Wautrecht, H.W. de Valk, A.C. Sales Luis, F.M. Parrot-Roulaud, K. S. Tan, I. Higgins, D. Garcon, M.J. Medrano, M. Candito, A.E. Evans, G. Andria, Plasma homocysteine as a risk factor for vascular disease. The European concerted Action Project, Jama, J. Am. Med. Assoc. 277 (1997) 1775–1781.
[35] S. Lee, P.5.a.006 Plasma homocysteine as a risk factor for Korean patients with vascular and Alzheimer's dementia, (n.d.) 1.
[36] C. Gaucher, A. Boudier, F. Dahboul, M. Parent, P. Leroy, S-nitrosation/denitrosation in cardiovascular pathologies: facts and concepts for the rational design of s-nitrosothiols, Curr. Pharm. Des. 19 (2013) 458, https://doi.org/10.2174/1381612811306030458.
[37] S. Moncada, Nitric OXIDE IN THE VASCULATURE: PHYSIOLOGY AND PATHOPHYsiology, Ann. N. Y. Acad. Sci. 811 (1997) 60–69, https://doi.org/10.1111/j.1749-6632.1997.tb51989.x.
[38] J.S. Stamler, D.I. Simon, J.A. Osborne, M.E. Mullins, O. Jaraki, T. Michel, D. J. Singel, J. Loscalzo, S-nitrosylation of proteins with nitric oxide: synthesis and characterization of biologically active compounds, Proc. Natl. Acad. Sci. U. S. A. 89 (1992) 444–448.
[39] J. Beurton, A. Boudier, A. Barozzi Seabra, N.E. Vrana, I. Clarot, P. Lavalle, Nitric oxide delivering surfaces: an overview of functionalization strategies and efficiency progress, Adv. Healthc. Mater. (2022) e2102692–e, https://doi.org/10.1002/adhm.202102692.
[40] C. Perrin-Sarrado, Y. Zhou, V. Salgues, M. Parent, P. Giummelly, I. Lartaud, C. Gaucher, S-Nitrosothiols as potential therapeutics to induce a mobilizable vascular store of nitric oxide to counteract endothelial dysfunction, (2020).
[41] J. Bonetti, Y. Zhou, M. Parent, I. Clarot, H. Yu, I. Fries-Raeth, P. Leroy, I. Lartaud, C. Gaucher, Intestinal absorption of S-nitrosothiols: permeability and transport mechanisms, Biochem. Pharmacol. 155 (2018) 21–31, https://doi.org/10.1016/j.bcp.2018.06.018.
[42] M. Parent, Y. Zhou, J. Bonetti, C. Perrin-Sarrado, I. Lartaud, A. Sapin-Minet, C. Gaucher, Antioxidant properties of S-nitrosoglutathione and nanotechnologies, Proceedings 11 (2019) 15, https://doi.org/10.3390/proceedings2019011015.
[43] H. Yu, P. Chaimbault, I. Clarot, Z. Chen, P. Leroy, Labeling nitrogen species with the stable isotope 15N for their measurement by separative methods coupled with mass spectrometry: a review, Talanta 191 (2019) 491–503, https://doi.org/10.1016/j.talanta.2018.09.011.
[44] E. Bramanti, V. Angeli, Z. Mester, A. Pompella, A. Paolicchi, A. D'Ulivo, Determination of S-nitrosoglutathione in plasma: comparison of two methods, Talanta 81 (2010) 1295–1299, https://doi.org/10.1016/j.talanta.2010.02.024.
[45] D. Tsikas, M. Schmidt, A. Böhmer, A.A. Zoerner, F.-M. Gutzki, J. Jordan, UPLC–MS/MS measurement of S-nitrosoglutathione (GSNO) in human plasma solves the S-nitrosothiol concentration enigma, J. Chromatogr. B 927 (2013) 147–157, https://doi.org/10.1016/j.jchromb.2013.01.023.
[46] B. Mayer, S. Pfeiffer, A. Schrammel, D. Koesling, K. Schmidt, F. Brunner, A new pathway of nitric oxide/cyclic GMP signaling involving S-nitrosoglutathione, J. Biol. Chem. 273 (1998) 3264–3270.
[47] T. Tominaga, A. Furrer, R. Henry, D. Dubourdieu, Identification of new volatile thiols in the aroma of Vitis vinifera L. var. Sauvignon blanc wines, Flavour, Fragr. J. 13 (1998) 159–162, https://doi.org/10.1002/(SICI)1099-1026(199805/06)13:3<159::AID-FFJ709>3.0.CO;2-7.
[48] J.H. Swiegers, R.L. Kievit, T. Siebert, K.A. Lattey, B.R. Bramley, I.L. Francis, E. S. King, I.S. Pretorius, The influence of yeast on the aroma of Sauvignon Blanc wine, Food Microbiol. 26 (2009) 204–211, https://doi.org/10.1016/j.fm.2008.08.004.
[49] B. Concejero, P. Hernandez-Orte, J. Astrain, B. Lacau, C. Baron, V. Ferreira, Evolution of polyfunctional mercaptans and their precursors during Merlot alcoholic fermentation, LWT – Food Sci. Technol. 65 (2016) 770–776, https://doi.org/10.1016/j.lwt.2015.09.018.
[50] T. Tominaga, D. Dubourdieu, A novel method for quantification of 2-Methyl-3-furanthiol and 2-furanmethanethiol in wines made from *Vitis vinifera* grape varieties, J. Agric. Food Chem. 54 (2006) 29–33, https://doi.org/10.1021/jf050970b.
[51] D.L. Capone, A. Barker, P.O. Williamson, I.L. Francis, The role of potent thiols in chardonnay wine aroma: potent thiols in chardonnay wine, Aust. J. Grape Wine Res. 24 (2018) 38–50, https://doi.org/10.1111/ajgw.12294.
[52] C. Camarasa, M. Ugliano, M. Nikolantonaki, R. Schneider, F. Cavelier, F. Cha, I. Œnologue, S. Delpech, Devant le jury composé de, (n.d.) 210.
[53] N. Dulsat-Serra, B. Quintanilla-Casas, S. Vichi, Volatile thiols in coffee: A review on their formation, degradation, assessment and influence on coffee sensory quality, Food Res. Int. 89 (2016) 982–988, https://doi.org/10.1016/j.foodres.2016.02.008.
[54] M.-L.-K. Cibaka, J. Gros, S. Collin, Revue sur les analogies et les différences relevées entre un cône de houblon et une baie de raisin : arômes soufrés et azotés, Biotechnol. Agron. Soc. Environ. (2017) 16.
[55] M.N. Lund, M.L. Andersen, Detection of thiol groups in beer and their correlation with oxidative stability, J. Am. Soc. Brew. Chem. 69 (2011) 163–169, https://doi.org/10.1094/ASBCJ-2011-0620-01.
[56] M.J. Wu, F.M. Clarke, P.J. Rogers, P. Young, N. Sales, P.J. O'Doherty, V. J. Higgins, Identification of a protein with antioxidant activity that is important for the protection against beer ageing, Int. J. Mol. Sci. 12 (2011) 6089–6103, https://doi.org/10.3390/ijms12096089.
[57] M.L. Andersen, M. Gundermann, B.P. Danielsen, M.N. Lund, Kinetic models for the role of protein thiols during oxidation in beer, J. Agric. Food Chem. 65 (2017) 10820–10828, https://doi.org/10.1021/acs.jafc.7b05012.
[58] J.J. Baert, J. De Clippeleer, B. Jaskula-Goiris, F. Van Opstaele, G. De Rouck, G. Aerts, L. De Cooman, Further elucidation of beer flavor instability: the potential role of cysteine-bound aldehydes, J. Am. Soc. Brew. Chem. 73 (2015) 243–252, https://doi.org/10.1094/ASBCJ-2015-0531-01.
[59] V. Ferreira, R. Lopez, The actual and potential aroma of winemaking grapes, Biomolecules 9 (2019) 818, https://doi.org/10.3390/biom9120818.
[60] A. Peña-Gallego, P. Hernández-Orte, J. Cacho, V. Ferreira, S-cysteinylated and s-glutathionylated thiol precursors in grapes A review, Food Chem. 131 (2012) 1–13, https://doi.org/10.1016/j.foodchem.2011.07.079.
[61] T. Dufourcq, R. Schneider, R. Renard, E. Serrano, Incidences du climat, du sol, de la date de récolte sur le potentiel aromatique du cépage Colombard en Gascogne Incidences of the climate, the soil, and the harvest date on Colombard aromatic potential in Gascony, in: 2006.Sun.

[62] X. Choné, Contribution à l'étude des terroirs de Bordeaux : étude des déficits hydriques modérés, de l'alimentation en azote et de leurs effets sur le potentiel aromatique des raisins de Vitis vinifera L. cv. Sauvignon blanc, These de doctorat, Bordeaux 2, 2001. http://www.theses.fr/2001BOR20917 (accessed February 10, 2022).

[63] D.W. Jeffery, Spotlight on varietal thiols and precursors in grapes and wines, Aust. J. Chem. 69 (2016) 1323, https://doi.org/10.1071/CH16296.

[64] C.P. des Gachons, Recherches sur le potentiel aromatique des raisins de Vitis vinifera L. Cv. Sauvignon blanc, Undefined. (2000). https://www.semanticscholar.org/paper/Recherches-sur-le-potentiel-aromatique-des-raisins-Gachons/2a22e8dc289dd395d257079e35f30dc7ee7923f6 (accessed February 10, 2022).

[65] I. Masneuf-Pomarède, M.-L. Murat, G. Naumov, T. Tominaga, D. Dubourdieu, Hybrids Saccharomyces cerevisiae X Saccharomyces bayanus var. uvarum having a high liberating ability of some sulfur varietal aromas of Vitis vinifera Sauvignon blanc wines, J. Int. Sci. Vigne Vin. 36 (2002) 205–212. 10.20870/oeno-one.2002.36.4.965.

[66] N. ANFANG, M. BRAJKOVICH, M. Goddard, Anfang N, Brajkovich M, Goddard MR.. Co-fermentation with Pichia kluyveri increases varietal thiol concentrations in Sauvignon Blanc. Aust J Grape Wine R 15: 1-8, Aust. J. Grape Wine Res. 15 (2008) 1–8. 10.1111/j.1755-0238.2008.00031.x.

[67] N.N. Sazhina, Determination of antioxidant activity of various bioantioxidants and their mixtures by the amperometric method, Russ. J. Bioorganic Chem. 43 (2017) 771–775, https://doi.org/10.1134/S1068162017070147.

[68] N. Fu, H. Wang, M. Li, G. Zheng, H. Zhang, S. Liang, Spectrofluorimetric determination of thiols in biological samples with a new fluorescent probe 3-maleimidylbenzanthrone, Anal. Lett. 38 (2005) 791–802, https://doi.org/10.1081/AL-200051025.

[69] L. Kukoc-Modun, M. Biocic, N. Radić, Determination of penicillamine, tiopronin and glutathione in pharmaceutical formulations by kinetic spectrophotometry, Acta Pharm. 71 (2021) 619–630, https://doi.org/10.2478/acph-2021-0038.

[70] H. Häkkinen, The gold–sulfur interface at the nanoscale, Nat. Chem. 4 (2012) 443–455, https://doi.org/10.1038/nchem.1352.

[71] J.C. Love, L.A. Estroff, J.K. Kriebel, R.G. Nuzzo, G.M. Whitesides, Self-assembled monolayers of thiolates on metals as a form of nanotechnology, Chem. Rev. 105 (2005) 1103–1170, https://doi.org/10.1021/cr0300789.

[72] E.C. Kritzinger, F.F. Bauer, W.J. du Toit, Role of glutathione in winemaking: A review, J. Agric. Food Chem. 61 (2013) 269–277, https://doi.org/10.1021/Jf303665z.

[73] S. Melnyk, M. Pogribna, I. Pogribny, R.J. Hine, S.J. James, A new HPLC method for the simultaneous determination of oxidized and reduced plasma aminothiols using coulometric electrochemical detection11This work was funded by a grant from the FDA-Office of Women's Health, J. Nutr. Biochem. 10 (1999) 490–497, https://doi.org/10.1016/S0955-2863(99)00033-9.

[74] L. Mateo-Vivaracho, J. Zapata, J. Cacho, V. Ferreira, Analysis, occurrence, and potential sensory significance of five polyfunctional mercaptans in white wines, J. Agric. Food Chem. 58 (2010) 10184–10194, https://doi.org/10.1021/jf101095a.

[75] D.L. Capone, R. Ristic, K.H. Pardon, D.W. Jeffery, Simple quantitative determination of potent thiols at ultratrace levels in wine by derivatization and high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) analysis, Anal. Chem. 87 (2015) 1226–1231, https://doi.org/10.1021/ac503883s.

[76] D. Giustarini, A. Milzani, I. Dalle-Donne, R. Rossi, Detection of S-nitrosothiols in biological fluids: A comparison among the most widely applied methodologies, J. Chromatogr. B. 851 (2007) 124–139, https://doi.org/10.1016/j.jchromb.2006.09.031.

[77] A. Roland, S. Delpech, L. Dagan, M.-A. Ducasse, F. Cavelier, R. Schneider, Innovative analysis of 3-mercaptohexan-1-ol, 3-mercaptohexylacetate and their corresponding disulfides in wine by stable isotope dilution assay and nano-liquid chromatography tandem mass spectrometry, J. Chromatogr. A. 1468 (2016) 154–163, https://doi.org/10.1016/j.chroma.2016.09.043.

[78] C. Bayle, C. Issac, R. Salvayre, F. Couderc, E. Caussé, Assay of total homocysteine and other thiols by capillary electrophoresis and laser-induced fluorescence detection: II. Pre-analytical and analytical conditions, J. Chromatogr. A 979 (2002) 255–260, https://doi.org/10.1016/S0021-9673(02)01504-2.

[79] E. Camera, M. Rinaldi, S. Briganti, M. Picardo, S. Fanali, Simultaneous determination of reduced and oxidized glutathione in peripheral blood mononuclear cells by liquid chromatography-electrospray mass spectrometry, J. Chromatogr. B. Biomed. Sci. App. 757 (2001) 69–78, https://doi.org/10.1016/s0378-4347(01)00081-0.

[80] A.F. Loughlin, G.L. Skiles, D.W. Alberts, W.H. Schaefer, An ion exchange liquid chromatography/mass spectrometry method for the determination of reduced and oxidized glutathione and glutathione conjugates in hepatocytes, J. Pharm. Biomed. Anal. 26 (2001) 131–142, https://doi.org/10.1016/S0731-7085(01)00402-2.

[81] C. Muscari, M. Pappagallo, D. Ferrari, E. Giordano, C. Capanni, C.M. Caldarera, C. Guarnieri, Simultaneous detection of reduced and oxidized glutathione in tissues and mitochondria by capillary electrophoresis, J. Chromatogr. B. Biomed. Sci. App. 707 (1998) 301–307, https://doi.org/10.1016/S0378-4347(97)00595-1.

[82] E. Beutler, O. Duron, B.M. Kelly, Improved method for the determination of blood glutathione, J. Lab. Clin. Med. 61 (1963) 882–888.

[83] M. Nikolantonaki, Identification of adducts between an odoriferous volatile thiol and oxidized grape phenolic compounds: kinetic study of adduct formation under chemical and enzymatic oxidation conditions | journal of agricultural and food chemistry, J. Agric. Food Chem. 2647–2656 (2012).

[84] T. ToMINAGA, Identification de l'acetate de 3-mercaptohexanol, compose aforte odeur de buis, intervenant dans l'arome des vins de Sauvignon, (n.d.) 4.

[85] S. Bailly, V. Jerkovic, J. Marchand-Brynaert, S. Collin, Aroma extraction dilution analysis of sauternes wines. key role of polyfunctional thiols, J. Agric. Food Chem. 54 (2006) 7227–7234, https://doi.org/10.1021/jf060814k.

[86] A.M. Svardal, M.A. Mansoor, P.M. Ueland, Determination of reduced, oxidized, and protein-bound glutathione in human plasma with precolumn derivatization with monobromobimane and liquid chromatography, Anal. Biochem. 184 (1990) 338–346, https://doi.org/10.1016/0003-2697(90)90691-2.

[87] J. Oliver Sass, W. Endres, Quantitation of total homocysteine in human plasma by derivatization to its N(O, S)-propoxycarbonyl propyl ester and gas chromatography–mass spectrometry analysis, J. Chromatogr. A 776 (1997) 342–347, https://doi.org/10.1016/S0378-4347(97)00080-7.

[88] M. Koller, H. Eckert, Derivatization of peptides for their determination by chromatographic methods, Anal. Chim. Acta. 352 (1997) 31–59, https://doi.org/10.1016/S0003-2670(97)00321-8.

[89] E. Sarrazin, S. Shinkaruk, T. Tominaga, B. Bennetau, E. Frérot, D. Dubourdieu, Odorous impact of volatile thiols on the aroma of young botrytized sweet wines: identification and quantification of new sulfanyl alcohols, J. Agric. Food Chem. 55 (2007) 1437–1444, https://doi.org/10.1021/jf062582v.

[90] P. Monostori, Determination of glutathione and glutathione disulfide in biological samples: an in-depth review - PubMed, J. Chromatogr. B. 877 (2009) 3331–3346, https://doi.org/10.1016/j.jchromb.2009.06.016.

[91] S.-C. Liang, H. Wang, Z.-M. Zhang, X. Zhang, H.-S. Zhang, Direct spectrofluorimetric determination of glutathione in biological samples using 5-maleimidyl-2-(m-methylphenyl) benzoxazole, Anal. Chim. Acta 451 (2002) 211–219, https://doi.org/10.1016/S0003-2670(01)01409-X.

[92] T. Inoue, J.R. Kirchhoff, Electrochemical detection of thiols with a coenzyme pyrroloquinoline quinone modified electrode, Anal. Chem. 72 (2000) 5755–5760, https://doi.org/10.1021/ac000716c.

[93] G.L. Ellman, Tissue sulfhydryl groups, Arch. Biochem. Biophys. 82 (1959) 70–77, https://doi.org/10.1016/0003-9861(59)90090-6.

[94] K. Kowalska, M. Zalewska, H. Milnerowicz, The application of capillary electrophoresis in the determination of glutathione in healthy women's blood, J. Chromatogr. Sci. 53 (2015) 353–359, https://doi.org/10.1093/chromsci/bmu035.

[95] K. Ngamchue, Rapid method for the quantification of reduced and oxidized glutathione in human plasma and saliva | analytical chemistry, Anal. Chem. 89 (2017) 2901–2908, https://doi.org/10.1021/acs.analchem.6b04186.

[96] X. Dai, Z.-F. Du, L.-H. Wang, J.-Y. Miao, B.-X. Zhao, A quick response fluorescent probe based on coumarin and quinone for glutathione and its application in living cells, Anal. Chim. Acta 922 (2016) 64–70, https://doi.org/10.1016/j.aca.2016.04.003.

[97] N. Nehra, V.D. Ghule, R.K. Tittal, Simpler fluorescent probe for homocysteine selective detection, J. Mol. Struct. 1250 (2022), 131755, https://doi.org/10.1016/j.molstruc.2021.131755.

[98] D. Fracassetti, N. Lawrence, A.G.J. Tredoux, A. Tirelli, H.H. Nieuwoudt, W.J. Du Toit, Quantification of glutathione, catechin and caffeic acid in grape juice and wine by a novel ultra-performance liquid chromatography method, Food Chem. 128 (2011) 1136–1142, https://doi.org/10.1016/j.foodchem.2011.04.001.

[99] R. Głowacki, J. Stachniuk, K. Borowczyk, H. Jakubowski, Quantification of homocysteine and cysteine by derivatization with pyridoxal 5'-phosphate and hydrophilic interaction liquid chromatography, Anal. Bioanal. Chem. 408 (2016) 1935–1941, https://doi.org/10.1007/s00216-016-9308-3.

[100] W. Jin, X. Li, N. Gao, Simultaneous determination of tryptophan and glutathione in individual rat hepatocytes by capillary zone electrophoresis with electrochemical detection at a carbon fiber bundle−Au/Hg dual electrode, Anal. Chem. 75 (2003) 3859–3864, https://doi.org/10.1021/ac0207022.

[101] J. Hodáková, J. Preisler, F. Foret, P. Kubáň, Sensitive determination of glutathione in biological samples by capillary electrophoresis with green (515nm) laser-induced fluorescence detection, J. Chromatogr. A 1391 (2015) 102–108, https://doi.org/10.1016/j.chroma.2015.02.062.

[102] C. Hellmuth, B. Koletzko, W. Peissner, Aqueous normal phase chromatography improves quantification and qualification of homocysteine, cysteine and methionine by liquid chromatography–tandem mass spectrometry, J. Chromatogr. B 879 (2011) 83–89, https://doi.org/10.1016/j.jchromb.2010.11.016.

[103] Z. Sun, N. Yang, C. Liu, R.S.T. Linforth, X. Zhang, I.D. Fisk, Aroma binding and stability in brewed coffee: a case study of 2-furfurylthiol, Food Chem. 295 (2019) 449–455, https://doi.org/10.1016/j.foodchem.2019.05.175.

[104] T. Tominaga, G. Guimbertau, D. Dubourdieu, Contribution of benzenemethanethiol to smoky aroma of certain vitis vinifera L. Wines, J. Agric. Food Chem. 51 (2003) 1373–1376, https://doi.org/10.1021/jf020756c.

[105] M.A. Raggi, R. Mandrioli, F. Bugamelli, C. Sabbioni, Comparison of analytical methods for quality control of pharmaceutical formulations containing glutathione, Chromatographia 46 (1997) 17–22, https://doi.org/10.1007/BF02490925.

[106] Z. Sun, K. Hayat, J. Yu, E. Karangwa, E. Duhoranimana, X. Zhang, S. Xia, Quantification of free 2-furfurylthiol in coffee brew using a prefabricated coffee model, Food Anal. Methods 11 (2018) 654–662, https://doi.org/10.1007/s12161-017-1034-8.

[107] B. Fedrizzi, G. Versini, I. Lavagnini, D. Badocco, G. Nicolini, F. Magno, Hyphenated gas chromatography–mass spectrometry analysis of 3-mercapto-hexan-1-ol and 3-mercaptohexyl acetate in wine, Anal. Chim. Acta 621 (2008) 38–43, https://doi.org/10.1016/j.aca.2007.10.040.

[108] B. Fedrizzi, G. Versini, I. Lavagnini, G. Nicolini, F. Magno, Gas chromatography–mass spectrometry determination of 3-mercaptohexan-1-ol and 3-mercaptohexyl acetate in wine: a comparison of headspace solid phase microextraction and solid phase extraction methods, Anal. Chim. Acta 596 (2007) 291–297, https://doi.org/10.1016/j.aca.2007.06.007.
[109] P. Darriet, T. Tominaga, V. Lavigne, J.-N. Boidron, D. Dubourdieu, Identification of a powerful aromatic component of Vitis vinifera L. var. sauvignon wines: 4-mercapto-4-methylpentan-2-one, Flavour, Fragr. J. 10 (1995) 385–392, https://doi.org/10.1002/ffj.2730100610.
[110] M. Ahmed, S.M. Youssef, H.S. El-Sayed, H.H. El-Sayed, F.M. Salama, M.H. Assem, Abd El-Salam, Novel bionanocomposite materials used for packaging skimmed milk acid coagulated cheese (Karish), Int. J. Biol. Macromol. 115 (2018) 1002–1011, https://doi.org/10.1016/j.ijbiomac.2018.04.165.
[111] S. Jaworski, M. Wierzbicki, E. Sawosz, A. Jung, G. Gielerak, J. Biernat, H. Jaremek, W. Łojkowski, B. Woźniak, J. Wojnarowicz, L. Stobiński, A. Małolepszy, M. Mazurkiewicz-Pawlicka, M. Łojkowski, N. Kurantowicz, A. Chwalibog, Graphene oxide-based nanocomposites decorated with silver nanoparticles as an antibacterial agent, Nanoscale Res. Lett. 13 (2018) 116, https://doi.org/10.1186/s11671-018-2533-2.
[112] M. Kachoei, A. Nourian, B. Divband, Z. Kachoei, S. Shirazi, Zinc-oxide nanocoating for improvement of the antibacterial and frictional behavior of nickel-titanium alloy, Nanomed 11 (2016) 2511–2527, https://doi.org/10.2217/nnm-2016-0171.
[113] M.A. Yassin, T.A. Elkhooly, S.M. Elsherbiny, F.M. Reicha, A.A. Shokeir, Facile coating of urinary catheter with bio–inspired antibacterial coating, Heliyon 5 (2019), https://doi.org/10.1016/j.heliyon.2019.e02986.
[114] S. Azlin-Hasim, M.C. Cruz-Romero, M.A. Morris, E. Cummins, J.P. Kerry, Spray coating application for the development of nanocoated antimicrobial low-density polyethylene films to increase the shelf life of chicken breast fillets, Food Sci. Technol. Int. Cienc. Tecnol. Los Aliment. Int. 24 (2018) 688–698, https://doi.org/10.1177/1082013218789224.
[115] W. Niu, X. Li, S.K. Karuturi, D.W. Fam, H. Fan, S. Shrestha, L.H. Wong, A.I.Y. Tok, Applications of atomic layer deposition in solar cells, Nanotechnology 26 (2015), 064001, https://doi.org/10.1088/0957-4484/26/6/064001.
[116] X. Meng, X.-Q. Yang, X. Sun, Emerging applications of atomic layer deposition for lithium-ion battery studies, Adv. Mater. Deerfield Beach Fla 24 (2012) 3589–3615, https://doi.org/10.1002/adma.201200397.
[117] G.Z. Tsogas, F.A. Kappi, A.G. Vlessidis, D.L. Giokas, Recent advances in nanomaterial probes for optical biothiol sensing: a review, Anal. Lett. 51 (2018) 443–468, https://doi.org/10.1080/00032719.2017.1329833.
[118] J. Kubavat, J. Thakarda, T. Tyagi, S. Bhowmik, P. Maity, Selective sensing of thiols by aryl iodide stabilized fluorescent gold cluster through turn-off excimer emission caused by ligand displacement, J. Chem. Sci. 133 (2021) 72, https://doi.org/10.1007/s12039-021-01944-z.
[119] Y. He, L. Zheng, Gold nanoparticle-catalyzed clock reaction of methylene blue and hydrazine for visual chronometric detection of glutathione and cysteine, ACS Sustain. Chem. Eng. 5 (2017) 9355–9359, https://doi.org/10.1021/acssuschemeng.7b02391.
[120] M.J. Farrell, R.J. Reaume, A.K. Pradhan, Visual detection of denatured glutathione peptides: a facile method to visibly detect heat stressed biomolecules, Sci. Rep. 7 (2017) 2604, https://doi.org/10.1038/s41598-017-02899-3.
[121] Y.-L. Cao, Y. Li, F. Zhang, J.-Z. Huo, X.-J. Zhao, Highly sensitive 'naked-eye' colorimetric detection of thiourea using gold nanoparticles, Anal. Methods 7 (2015) 4927–4933, https://doi.org/10.1039/C5AY00558B.
[122] S. Jongjinakool, K. Palasak, N. Bousod, S. Teepoo, Gold nanoparticles-based colorimetric sensor for cysteine detection, Energy Procedia 56 (2014) 10–18, https://doi.org/10.1016/j.egypro.2014.07.126.
[123] Q. Qian, J. Deng, D. Wang, L. Yang, P. Yu, L. Mao, Aspartic acid-promoted highly selective and sensitive colorimetric sensing of cysteine in rat brain, Anal. Chem. 84 (2012) 9579–9584, https://doi.org/10.1021/ac3024608.
[124] M. Li, S. Mao, S. Wang, H.-F. Li, J.-M. Lin, Chip-based SALDI-MS for rapid determination of intracellular ratios of glutathione to glutathione disulfide, Sci. China Chem. 62 (2019) 142–150, https://doi.org/10.1007/s11426-018-9327-7.
[125] D. Wan, M. Gao, Y. Wang, P. Zhang, X. Zhang, A rapid and simple separation and direct detection of glutathione by gold nanoparticles and graphene-based MALDI–TOF-MS, J. Sep. Sci. 36 (2013) 629–635, https://doi.org/10.1002/jssc.201200766.
[126] O. Mompó-Roselló, M. Vergara-Barberán, E.F. Simó-Alfonso, J.M. Herrero-Martínez, In syringe hybrid monoliths modified with gold nanoparticles for selective extraction of glutathione in biological fluids prior to its determination by HPLC, Talanta 209 (2020), 120566, https://doi.org/10.1016/j.talanta.2019.120566.
[127] M. Berthou, A. Pallotta, J. Beurton, T. Chaigneau, A. Athanassiou, C. Marcic, E. Marchioni, A. Boudier, I. Clarot, Gold nanostructured membranes to concentrate low molecular weight thiols, a proof of concept study, J. Chromatogr. B 1198 (2022), 123244, https://doi.org/10.1016/j.jchromb.2022.123244.
[128] V. Baldim, A. Ismail, P. Taladriz-Blanco, S. Griveau, M.G. de Oliveira, F. Bedioui, Amperometric quantification of s-nitrosoglutathione using gold nanoparticles: a step toward determination of s-nitrosothiols in plasma, Anal. Chem. 88 (2016) 3115–3120, https://doi.org/10.1021/acs.analchem.5b04035.
[129] M. Markina, N. Stozhko, V. Krylov, M. Vidrevich, K.h. Brainina, Nanoparticle-based paper sensor for thiols evaluation in human skin, Talanta 165 (2017) 563–569, https://doi.org/10.1016/j.talanta.2017.01.012.
[130] C.-C. Shen, W.-L. Tseng, M.-M. Hsieh, Selective extraction of thiol-containing peptides in seawater using Tween 20-capped gold nanoparticles followed by capillary electrophoresis with laser-induced fluorescence, J. Chromatogr. A 1220 (2012) 162–168, https://doi.org/10.1016/j.chroma.2011.11.057.
[131] C.-W. Chang, W.-L. Tseng, Gold nanoparticle extraction followed by capillary electrophoresis to determine the total, free, and protein-bound aminothiols in plasma, Anal. Chem. 82 (2010) 2696–2702, https://doi.org/10.1021/ac902342c.
[132] Y. Zhang, W. Chen, Y. Zhang, Y. Zhang, L. Zhu, P. He, Q. Wang, Sensitive analysis of reduced glutathione in bacteria and HaCaT cells by capillary electrophoresis via online pre-concentration of transient trapping combined with the dynamic pH junction mode, New J. Chem. 41 (2017) 12920–12929, https://doi.org/10.1039/C7NJ02184D.
[133] M. Wang, Z. Chen, X. Jing, H. Zhou, Y. Wang, J. Ye, Q. Chu, Tween 20-capped gold nanoparticles for selective extraction of free low-molecular-weight thiols in saliva followed by capillary electrophoresis with contactless conductivity detection, J. Chromatogr. B 1176 (2021), 122756, https://doi.org/10.1016/j.jchromb.2021.122756.
[134] A. Çifteci, S.E. Çelik, R. Apak, Gold-nanoparticle based turn–on fluorometric sensor for quantification of sulfhydryl and disulfide forms of biothiols: measurement of thiol/disulfide homeostasis, Anal. Lett. 55 (2022) 648–664, https://doi.org/10.1080/00032719.2021.1958830.
[135] J. Ju, R. Zhang, W. Chen, Photochemical deposition of surface-clean silver nanoparticles on nitrogen-doped graphene quantum dots for sensitive colorimetric detection of glutathione, Sens. Actuat. B Chem. 228 (2016) 66–73, https://doi.org/10.1016/j.snb.2016.01.007.
[136] A. Kapur, Self-assembled gold nanoparticle-fluorescent protein conjugates as platforms for sensing thiolate compounds via modulation of energy transfer quenching | bioconjugate chemistry, Bioconjug. Chem. 28 (2017) 678–687, https://doi.org/10.1021/acs.bioconjchem.7b00006.
[137] Y.-L. Luo, X.-C. Huang, W.-M. Tu, H.-Y. Hsu, Differential in situ sensing of extra- and intracellular glutathione by a novel redox-responsive silica matrix-Au nanoprobe, Anal. Chim. Acta 902 (2016) 196–204, https://doi.org/10.1016/j.aca.2015.11.018.
[138] H.-Q. Chen, F. Yuan, L. Wang, Simple and sensitive turn-on luminescent detection of biothiols based on energy transfer between green-emitting upconversion nanocrystals and gold nanoparticles, Anal. Methods 5 (2013) 2873, https://doi.org/10.1039/c3ay40105g.
[139] J. Xu, H. Yu, Y. Hu, M. Chen, S. Shao, A gold nanoparticle-based fluorescence sensor for high sensitive and selective detection of thiols in living cells, Biosens. Bioelectron. 75 (2016) 1–7, https://doi.org/10.1016/j.bios.2015.08.007.
[140] A. Sangsuwan, B. Narupai, P. Sae-ung, S. Rodtamai, N. Rodthongkum, V. P. Hoven, Patterned poly(acrylic acid) Brushes containing gold nanoparticles for peptide detection by surface-assisted laser desorption/ionization mass spectrometry, Anal. Chem. 87 (2015) 10738–10746, https://doi.org/10.1021/acs.analchem.5b00734.
[141] F. Ghasemi, M.R. Hormozi-Nezhad, M. Mahmoudi, A colorimetric sensor array for detection and discrimination of biothiols based on aggregation of gold nanoparticles, Anal. Chim. Acta 882 (2015) 58–67, https://doi.org/10.1016/j.aca.2015.04.011.
[142] E. Jeyasekaran, S. Venkatachalam, Colorimetric detection of cysteine based on dispersion–aggregation mechanism of chitosan stabilized gold nanoparticles, Can. J. Chem. 97 (2019) 233–237, https://doi.org/10.1139/cjc-2018-0258.
[143] J. Wang, M. Jie, H. Li, L. Lin, Z. He, S. Wang, J.-M. Lin, Gold nanoparticles modified porous silicon chip for SALDI-MS determination of glutathione in cells, Talanta 168 (2017) 222–229, https://doi.org/10.1016/j.talanta.2017.02.041.
[144] Y. Chen, X. Qin, C. Yuan, Y. Wang, Switch on fluorescence mode for determination of L-cysteine with carbon quantum dots and Au nanoparticles as a probe, RSC Adv. 10 (2020) 1989–1994, https://doi.org/10.1039/C9RA09019C.
[145] S. Tanwar, B. Sharma, V. Kaur, T. Sen, White light emission from a mixture of silicon quantum dots and gold nanoclusters and its utilities in sensing of mercury ions and thiol containing amino acid, RSC Adv. 9 (2019) 15997–166. 10.1039/c9ra02012h.
[146] A.M. Hafez, B.W. Wenclawiak, Development of a new porous gold SPME fiber for selective and efficient extraction of dodecanethiol followed by GC–MS analysis, Anal. Bioanal. Chem. 405 (2013) 1753–1758, https://doi.org/10.1007/s00216-012-6580-8.
[147] A.M. Hafez, Q.T. Hua, M.S.S. Adam, Time-of-flight secondary ion mass spectrometry and gas chromatography–mass spectrometry studies of alkanethiol self-assembled monolayers on nanoporous gold surfaces, Surf. Interface Anal. 53 (2021) 21–30, https://doi.org/10.1002/sia.6869.
[148] H. Zhang, Z. Jia, Development of fluorescent FRET probes for "Off-On" detection of L-cysteine based on gold nanoparticles and porous silicon nanoparticles in ethanol solution, Sensors 17 (2017) 520, https://doi.org/10.3390/s17030520.
[149] Y. Bu, G. Zhu, S. Li, R. Qi, G. Bhave, D. Zhang, R. Han, D. Sun, X. Liu, Z. Hu, X. Liu, Silver-nanoparticle-embedded porous silicon disks enabled SERS signal amplification for selective glutathione detection, ACS Appl. Nano Mater. 1 (2018) 410–417, https://doi.org/10.1021/acsanm.7b00290.
[150] C. Li, DNA-functionlized silver nanoclusters as label-free fluorescent probe for the highly sensitive detection of biothiols and acetylcholinesterase activity, (2017) 8.
[151] S. Hajizadeh, K. Farhadi, M. Forough, R. Molaei, Silver nanoparticles in the presence of Ca2+ as a selective and sensitive probe for the colorimetric detection of cysteine, Anal. Methods 4 (2012) 1747-, https://doi.org/10.1039/c2ay05848k.
[152] Y. Zhou, W. Huang, Y. He, pH-Induced silver nanoprism etching-based multichannel colorimetric sensor array for ultrasensitive discrimination of thiols, Sens. Actuat. B Chem. 270 (2018) 187–191, https://doi.org/10.1016/j.snb.2018.05.025.

[153] Z. Wu, W. Li, J. Chen, C. Yu, A graphene quantum dot-based method for the highly sensitive and selective fluorescence turn on detection of biothiols, Talanta (2014), https://doi.org/10.1016/j.talanta.2013.11.065.
[154] J.Y. Liang, L. Han, S.G. Liu, Y.J. Ju, N.B. Li, H.Q. Luo, Carbon dots-based fluorescent turn off/on sensor for highly selective and sensitive detection of Hg2+ and biothiols, Spectrochim. Acta. A. Mol. Biomol. Spectrosc. 222 (2019), 117260, https://doi.org/10.1016/j.saa.2019.117260.
[155] H. Fu, Z. Ji, X. Chen, A. Cheng, S. Liu, P. Gong, G. Li, G. Chen, Z. Sun, X. Zhao, F. Cheng, J. You, A versatile ratiometric nanosensing approach for sensitive and accurate detection of Hg2+ and biological thiols based on new fluorescent carbon quantum dots, Anal. Bioanal. Chem. 409 (2017) 2373–2382, https://doi.org/10.1007/s00216-017-0183-3.
[156] S. Chen, C.-H. Xu, Y.-L. Yu, J.-H. Wang, Multichannel fluorescent sensor array for discrimination of thiols using carbon dot–metal ion pairs, Sens. Actuat. B Chem. 266 (2018) 553–560, https://doi.org/10.1016/j.snb.2018.03.174.
[157] A. Mehta, A. Mishra, S. Basu, Optical detection of thiol drugs by core-shell luminous carbon dots—gold nanoparticles system, Plasmonics (2018), https://doi.org/10.1007/s11468-018-0744-0.
[158] Z. Yan, X. Qu, Q. Niu, C. Tian, C. Fan, B. Ye, A green synthesis of highly fluorescent nitrogen-doped graphene quantum dots for the highly sensitive and selective detection of mercury(II) ions and biothiols, (2016). 10.1039/C5AY03208C.
[159] D. Wu, G. Li, X. Chen, N. Qiu, X. Shi, G. Chen, Z. Sun, J. You, Y. Wu, Fluorometric determination and imaging of glutathione based on a thiol-triggered inner filter effect on the fluorescence of carbon dots, Microchim. Acta 184 (2017) 1923–1931, https://doi.org/10.1007/s00604-017-2187-2.
[160] H. Xu, J. Xiao, B. Liu, S. Griveau, F. Bedioui, Enhanced electrochemical sensing of thiols based on cobalt phthalocyanine immobilized on nitrogen-doped graphene, Biosens. Bioelectron. 66 (2015) 438–444, https://doi.org/10.1016/j.bios.2014.12.011.
[161] A.B. Ganganboina, A. Dutta Chowdhury, R. Doong, N-doped graphene quantum dots-decorated V2O5 nanosheet for fluorescence turn off–on detection of cysteine, ACS Appl. Mater. Interfaces 10 (2018) 614–624, https://doi.org/10.1021/acsami.7b15120.
[162] S. Dou, J. Du, Q. Zhu, Z. Wang, Y. Wang, Q. Chen, N. Lu, Au nanoparticles/ZnO nanorods as SALDI-MS substrate for on-plate enrichment and detection of glutathione in real samples, Sens. Actuat. B Chem. 335 (2021), 129709, https://doi.org/10.1016/j.snb.2021.129709.
[163] C.-K. Chiang, N.-C. Chiang, Z.-H. Lin, G.-Y. Lan, Y.-W. Lin, H.-T. Chang, Nanomaterial-based surface-assisted laser desorption/ionization mass spectrometry of peptides and proteins, J. Am. Soc. Mass Spectrom. 21 (2010) 1204–1207, https://doi.org/10.1016/j.jasms.2010.02.028.
[164] M. Sabela, S. Balme, M. Bechelany, J.-M. Janot, K. Bisetty, A review of gold and silver nanoparticle-based colorimetric sensing assays, Adv. Eng. Mater. 19 (2017) 1700270, https://doi.org/10.1002/adem.201700270.
[165] A. Pallotta, A. Boudier, B. Creusot, E. Brun, C. Sicard-Roselli, R. Bazzi, S. Roux, I. Clarot, Quality control of gold nanoparticles as pharmaceutical ingredients, Int. J. Pharm. 569 (2019), 118583, https://doi.org/10.1016/j.ijpharm.2019.118583.
[167] K. Saha, S.S. Agasti, C. Kim, X. Li, V.M. Rotello, Gold nanoparticles in chemical and biological sensing, Chem. Rev. 112 (2012) 2739–2779, https://doi.org/10.1021/cr2001178.
[168] F. Gao, Q. Ye, P. Cui, X. Chen, M. Li, L. Wang, Selective “turn-on” fluorescent sensing for biothiols based on fluorescence resonance energy transfer between acridine orange and gold nanoparticles, Anal. Methods 3 (2011) 1180, https://doi.org/10.1039/c1ay05073g.
[169] M. Kiguchi, S. Miura, T. Takahashi, K. Hara, M. Sawamura, K. Murakoshi, Conductance of single 1,4-benzenediamine molecule bridging between Au and Pt electrodes, J. Phys. Chem. C 112 (2008) 13349–13352, https://doi.org/10.1021/jp806129u.
[171] L. Wei, Y. Song, P. Liu, K. Xuejun, Polystyrene nanofibers capped with copper nanoparticles for selective extraction of glutathione prior to its determination by HPLC, Microchim. Acta 185 (2018) 321, https://doi.org/10.1007/s00604-018-2845-z.