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Review Article

Innovative Approaches for the Extraction, Purification, and Quantification of Polyphenols: A Comprehensive Review

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ABSTRACT

Polyphenols are one of the well-known phytochemicals and exist as secondary metabolites in natural products and show numerous physiological effects in all the living organisms due to the presence of simple phenols, aromatic acids, lignans, flavonoids and other bioactive compounds. They prevent several degenerative diseases like cancer, cardiovascular and others hence increased the interest in foods, cosmetics and pharmaceutical industries. The development of an affordable and cost-effective process for extraction, purification, characterization and quantification of polyphenolics proved challenging because to their complex matrix, structural variety, and interactions with other cellular components. Organic solvents and/or water are the main solvents used to extract, isolate and purify the polyphenols using several methods like MAE, UAE, solid phase extraction, liquid-liquid extraction and purification techniques. Using chemical procedures such as spectrophotometry, chromatography and electrochemical methods, we will be able to detect the presence of phenolics individually and determine their total quantity; bio-analytical techniques are used for clinical samples. This review's primary goal is to discuss the modern methods of extraction, purification and separation, identification and quantification of phenolics from plant materials and summarize the recent developments for the analysis of clinical samples and various metabolic pathways of polyphenolics in mammalians.

Keywords: Analysis of Clinical samples, Electrochemical methods, Fractionation, Metabolism, Ultrasonic and Microwave assisted extraction.

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INTRODUCTION

A broad family of naturally occurring substances known as polyphenols are produced as secondary metabolites from plants (obtained from fruits, flowers, tea, wine and other plant parts) and protect the plants from stress, such as UV-radiation, infections, cuts etc. The complex polyphenols are known as tannin's (Bravo, 1998; Payra *et al.*, 2016). The evidence that all dietary polyphenols are useful in preventing common diseases, cancer, neurodegenerative diseases, gastrointestinal problems, and other conditions is mostly supported by epidemiological, clinical, and nutritional investigations (Pandey and Rizvi, 2009). Bioactive polyphenols exhibits blood pressure lowering, antioxidant, bacteriostatic, free radical scavenging in anti-inflammatory, anti-aging, anti-tumor, anti-viral, apoptotic, and anti-oxidation properties (Zhou *et al.*, 2019). Almost every kind of food and agro-industrial leftovers contains polyphenols (Nazzaro *et al.*, 2012). Increased consumption of polyphenols from fruits and vegetables has been strongly linked to a lower risk of acquiring degenerative diseases, cardiovascular disease, diabetes, and inflammatory disorders (Zhang and Taso, 2016). Plant phenols are divided into two types: Poly gallols and poly flavanols. Phenolic carboxylic acids and ester bonds make up the polyols' central structure (Behboodi-Sadabad *et al.*, 2017). Polyphenols are transformed into tannins by aerobic fermentation. The oxidized polyphenols in black tea are responsible for pungency, colour, briskness, taste and strength of the black tea infusion (Vasisht, 2004). The intake of polyphenol rich plants are much useful for humans, animals and will prevent the cardiovascular and cancer problems (Turati *et al.*, 2015).

The phytochemical profile of the medication is guided by spectroscopic or chromatographic fingerprint profiles of polyphenols for the purpose of determining the quantity and quality of the marker compound(s) (Kadam *et al.*, 2019). The estimation of polyphenols has been done by various techniques like Nuclear Magnetic Resonance (NMR), Near-Infrared (NIR)

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spectroscopy (Min and Peigen, 1991), High Performance Thin Layer Chromatography (HPTLC) (Lee and Choon-Nam Ong, 2000), High Performance Liquid Chromatography (HPLC), Liquid Chromatography-Mass Spectroscopy (LC-MS) (Ding *et al.*, 1999), High Performance Capillary Electrophoresis (HPCE) (Goto *et al.*, 1996). The literature suggested that the methods like TLC (Thin Layer Chromatography), NIR (Near Infrared) spectroscopy, HPLC-DAD (High Performance Liquid Chromatography-Diode Array Detector) etc., used for the quantification of phenols from the medical plants (Beecher *et al.*, 1999; Alam Zeb, 2015). RP-HPLC is a technique that can be used for the separation of complex mixtures (Bhatia *et al.*, 2019). The primary benefits of FT-IR include its minimal sample requirement either Micrograms (µg) or even Nanograms (ng), rapid analysis and absence of time-consuming sample pre-treatment (Dettmer *et al.*, 2007). The concentration of phenolic compounds seems to vary within the same fruit type depending on the season, diversity, climatic conditions, plant illness, type of soil, location, maturity and post-harvest treatment practices (Caruso *et al.*, 2015). Simple and complex phenols are identified using Gas Chromatography Mass Spectrometry (GC-MS) (Tasioula-Margari and Tsabolatidou, 2015). Some classes of phenolic compounds are shown in Table 1 (Ajila *et al.*, 2010).

History

Scheele C. W. and Vauquelin L. N. started the study of natural chemistry, which included phenols, and found that gallic acid was the first molecule discovered in addition to simple organic acids. The term polyphenols was used in the year 1894. A considerable research on plant phenols can be occurred in the 19th century and polyphenols began in 1950. In 1976, the quantity of polyphenols in the foods was estimated using chromatography of thin stack (TLC) and later in 1992, studied the total content in aglycones from 5 flavonoids and flavones in fruits, vegetables and tea (Vacek *et al.*, 2010).

Phenolic Extraction

The amount of phenolic extract produced will depend on the extraction solvent(s) used, which can include alcohols, water, acetone, ethyl acetate and their combinations, time and temperature, but it will be vary from one sample to another (Garcia-Salas *et al.*, 2010; Pinelo *et al.*, 2008).

Preparation of Sample

In human diet, plant foods and beverages are used for major source of phenolics. Based on sample matrix nature and chemical properties of the phenols, the preparation and extractions are varied. In few preparations of sample, the plant samples must be dry by using different drying techniques. To achieve the desired particle size, dried materials are ground or milled, while liquid samples are purified, filtered, and centrifuged as necessary, all with the aid of a separation system. When the particle size of phenolics is smaller, then the yield of extract is high and increases the enzymatic action. For instance, the defatted and grounded seeds of grapes using hexane as solvent simplify the phenolic extraction. In general, seeds are milled into small particles is advisable (Sejali and Anuar, 2011).

Factors Affecting on Extraction Process

Type of solvent

The various extraction solvents that are utilized have a direct impact on the activities of the antioxidants that are extracted, primarily polyphenolics (Chavan *et al.*, 2001). The extraction technique and solvent have a major impact on the yield of the extracted chemicals (Goli *et al.*, 2005; Sun and Chi-Tang Ho, 2005). The antioxidant activity of polyphenols is higher than natural antioxidants when they are extracted with ethyl acetate. Excess time of extraction may improve the chances of oxidation of phenolics which was prevented by adding reducing agents to the solvent system (Naczk and Shahidi, 2006).

pH

The pH plays a vital role in the extraction process of phenolics. To prevent the oxidation of phenolics, the pH of extraction solution must be low. On the basis of source and nature of polyphenols, the extraction medium pH will be varied (Chetan and Malleshi, 2007).

Types of Extraction

Extraction of Phenolic acids

Phenolics are existed in plants as free esters or glycosylated forms (Harukaze *et al.*, 1999). The best conditions for extracting the phenolic compounds from the plant material are refluxing at 80ºC with 80% methanol for 15 min, adjusting the pH to 2 with dilute HCl and use the ether to extract the free phenolic acids. The prepared ethereal extract is neutralized and dissolve in 2M NaOH under inert gas like nitrogen. The extract is again acidified to pH 2 following alkaline hydrolysis. The residual aqueous fraction was

Table 1: Types of Naturally occurring Polyphenolics.

Class	Structure
Bioflavonoids	$(C_6\text{-}C_3)_2$
Condensed tannins	$(C_6\text{-}C_3)_n$, $(C_6\text{-}C_3\text{-}C_6)_n$
Flavonoids, Isoflavonoids	$C_6\text{-}C_1\text{-}C_6$
Hydroxy cinnamic acids, Phenylpropanoids	$C_6\text{-}C_1$
Hydroxybenzoic acids	C_6
Lignans, Neolignane	$C_6\text{-}C_3\text{-}C_6$
Lignin	$(C_6\text{-}C_3\text{-}C_6)_2$
Naphthoquinones	$C_6\text{-}C_3$
Xanthones	$C_6\text{-}C_4$

mixed with 6M HCl and heated to 100ºC for 1 hr while under N_2 gas to liberate the phenolic acids from their glycosylated forms. Phenolic acids can also be extracted from plant products using ethanol or a combination of water with other polar solvents like chloroform, acetone and methanol (Stalikas, 2007).

Extraction of Flavonoids

Flavonoids are found to be bioactive compounds in all variety of plants (Biesaga, 2011). Often, the flavonoidal glycosides are hydrolyzed into the aglycones at 80ºC for 2 hr while being treated with HCl in a nitrogen atmosphere. The flavonoids are then extracted using 50% methanol, and enough ascorbic acid is added to avoid oxidation.

Extraction of Anthocyanin/Proanthocyanidin

The most prevalent pigments found in nature are known as Anthocyanins and are extracted using acidified solvents such as water, methanol, ethanol, acetone, or a combination of these solvents (Patil *et al*., 2009). During the process of extraction with acids, the solvent acts to rupture the cell membranes and release anthocyanins. Methanol is commonly used solvent for effective extraction of anthocyanins (Bridgers *et al*., 2010). Sulphur water (aqueous SO_2) has been utilized in addition to acidified solvents, to extract anthocyanins (Ju and Howard, 2005). Proanthocyanidins belongs to a group of polymeric polyphenols and are known as concentrated tannins and are found primarily in grapes, sea bark, cider, sorghum, pine bark, hops, mangosteen pericarp, berries, apple juice, malt and chocolates. Organic solvents like methanol, ethanol and acetone are generally used for effective extraction of proanthocyanidins (Hernández-Jiménez *et al*., 2012; Pekic *et al*., 1998). The extraction process of polyphenolics typically depends on solvents used for extraction. This extraction process is complicated and might result in complex errors in analytical methods because it required a lot of solvent(s) and degrades the target phytochemicals. Advanced polyphenol extraction methods, such as SLE, PLE, SFE, UAE, MAE, UF, and enzyme-assisted extraction, have been developed to prevent such issues.

Solid-Liquid Extraction (SLE)

It is among the simplest techniques for phenolic extraction. It consists of two steps. In the step I, the extraction with various solvents like methanol, ethanol, acetone, or in combination was used. Fractionation by liquid-liquid extraction is the step II followed by column chromatography. The solubility of phenolic compounds can be altered based on the chemical nature and complex formation of phenolics with other compounds (carbohydrates and proteins). Some of the non-phenolic and other compounds are also extracted by SLE. Other extension processes may be involved to remove them which lead to increase in cost for extraction and potential losses of the analyte (Baydar *et al*., 2004; Lapornik *et al*., 2005; Alonso-slaces *et al*., 2005).

Pressurized Liquid Extraction (PLE)

Pressurized liquid extraction is a novel technique for the extraction of polyphenols, also known as accelerated solvent extraction, at the high temperature which is above the boiling point using organic solvents. With the use of compressed gas, the extraction cell is filled with a solid sample and extracted using a suitable solvent at high temperatures (40-200ºC) and pressures (500-3000 psi) for a brief amount of time (5-15 min). The sample extract is then collected into a collection vial. To increase extraction kinetics, improve the solvent diffusivity by accelerating temperature to high. This method of extraction is highly suitable for thermally stable organic compounds. PLE

Table 2: Phenolic compounds extracted from plant materials by SCFE techniques.

Sample	Phenolic class	Temperature (ºC)	Time (min)	Pressure(bar)	Modifier
Baccharis dracunculifolia leaves	Phenolic compounds	40-60	--	200, 300, 400	----
Bitter guard	Flavonoids	30-50	40-60	250, 300, 350	Ethanol
Bupleurum roots	Phenolic contents	40	--	50, 100, 150, 200	----
Black elder and marc of grape	Phenolic contents	40	--	150, 350	Ethanol
Guava seed	Phenolic contents	40, 50, 60	120	100, 200, 300	Ethyl Acetate and Ethanol
PecahKaca	Flavonoids	40, 50, 60	40, 60, 80	100, 150, 200	Ethanol
Pistachio hulls	Phenolic contents	35, 45, 55	15, 25, 40	100, 200, 350	Methanol
Spearmint leaves	Flavonoids	40, 50, 60	30, 60, 90	100, 200, 300	Ethanol
Theobroma cacao hulls	Phenolic compounds	50	--	100, 200	Methanol and Acetone
Wheat germ	Phenolic contents	40, 60	10, 60	148, 602	----

-- = resembles not mentioned Time, ---- = resembles no modifiers requires less time, less solvent and less sample in total (Richter *et al.*, 1996; Kaufmann and Christen, 2002).

Supercritical Fluid Extraction (SCFE)

The substance will exist in a vapour-liquid equilibrium state known as the critical point at a specific temperature and pressure. SCF is a heavy liquid that is formed at a critical point of pressure and temperature with a gas-piercing ability, making SCF considered an effective and selective solvent. This makes it an efficient and successful method of extracting phenolics (Naahar *et al.*, 2005). Supercritical CO_2 is the most widely used SCF; ethane, butane, pentane, nitrous oxide, ammonia, trifluoro methane, and water are some additional SCFs that are also utilized (Palma and Taylor, 1999; Murga *et al.*, 2000). Supercritical CO_2 is a non-toxic and safe approach with a low critical temperature. It also lessens the chance of deterioration brought on by air and light. The CO_2 mixture's critical temperature rises with the addition of the co-solvent. It is also possible to extract the high boiling and thermally stable compounds using the SCF method at comparatively moderate temperatures (Foster *et al.*, 1991; Chafer *et al.*, 2004; Adil *et al.*, 2007). Optimized conditions for extraction of polyphenols by SCFE are mentioned in Table 2 (Khoddmi *et al.*, 2013).

Ultrasonic Assisted Extraction (UAE)

It is a tried-and-true technique for mild environments based on the phenomena of acoustic cavitations, which uses ultrasonic radiation as a potential energy aid to have a major impact on the rate at which different physical or chemical processes react (Choi *et al.*, 1998; Chemat *et al.*, 2008; Luque-Garcia and Luque de Castro, 2003). UAE has two advantages: 1) capability increasing the extraction of compounds and 2) reducing the time for extraction. It's a safe, effective, affordable, and environmentally friendly method. There are two drawbacks to it: 1) the ultrasonic energy is not distributed uniformly and 2) its power decreases over time. UAE method was developed to extract ginsenosides and polyphenols from apple pomace (Virot *et al.*, 2010; Wu *et al.*, 2001). Some of the developed methods have been shown in Table 3 (Khoddmi *et al.*, 2013).

Table 3: Biologically Active Compounds Extraction using UAE.

Sample	Solvent	Extraction time (min)	Phenolic class	Yield (mg GAA [b] /g)
Galla chinensis	Ethanol 70%	40	Tannin	491. 2
Orange peel	Ethanol 80%	30	PC [a]	2. 758
Satsuma mandarin peel	Methanol 80%	60	Hesperidin	1. 446
Soybeans	Ethanol 40-60%	20	Isoflavones	1. 353
Sunflower meal	Acetone 80%	30	PC [a]	30. 93

[a] Phenolic Content; [b] Gallic Acid Analog.

Table 4: Ideal Conditions for employing MAE to Extract Phenolics from Plant Foods.

Plant	Analyte	Solvent	Time (min)	Temperature (°C)	Power (w)	Solvent/ sample(mL/g)
Angelicae sinensis	Ferulic acid	90% Ethanol	9	---	850	6
Fagopyrum esculentum	TPC	50% Ethanol	15	150	---	50
Green tea	Flavanols	Water	30	80	600	20
Ipomoea batatas	TPC	53% Ethanol	2. 05	---	302	30
Melilotus officinalis (Linn).	Coumarin	50% Ethanol	5	50	100	20
Phaseolus vulgaris	TPC	50% Ethanol	15	150	---	49
Saussurea medusa	Flavonoids	80% Ethanol	60	80	1200	50
Spices	Phenolic acids	50% Ethanol	18	50	200	20
Tea	Polyphenols	60% Ethanol	10	80	600	12
Vanilla beans Radix	Vanillin	70% Ethanol	20	---	150	25
Vitis vinifera	TPC Flavonoids	100% Methanol	60	110	60	5

TPC = Total Phenolic Content

Microwave Assisted Extraction (MAE)

Since 1960s, microwaves have been used extensively in studies on secondary plant metabolites. Due to its rapid extraction rate, maximal extraction capacity, and little solvent consumption especially for constituents that are thermolabile, Microwave Aided Extraction (MAE) is one of the most sophisticated methods for extracting plant polyphenols (Chee *et al*., 1996). In this technique scientists are using non-ionizing electromagnetic waves in the range of 300 MH_Z to 300 GH_Z to produce a molecular motion by migration of ions and rotation of dipoles (Letellier and Budzinski, 1999; Camel, 2001). The core principle of the MAE approach is the direct effect of microwaves on molecules via dipole rotation and ionic conduction. If the polyphenols have a persistent dipole moment, they will absorb microwave radiation very well, which will cause the temperature to increase quickly and the extraction process to be completed quickly (Eskilsson and Bjorklund, 2000; Venkatesh and Raghavan, 2004; Gfrerer and Lankmayr, 2005). The solvent's polarity, solubility, dissipation factors and dielectric constant are the main physical parameters that go into the MAE. The kind of plant material to be extracted and the solvent system being utilized both affect the extraction rate (Proestos *et al*., 2006). The MAE process is used to extract polyphenols from vanilla, radix, tea leaves and flax seeds (Pan *et al*., 2003). Some of the MAE developed methods are shown in Table 4 (Khoddmi *et al*., 2013).

Ultrafiltration (UF)

Ultrafiltration is a type of membrane separation method for the separation and purification of polyphenols (Hossain, 2005). One of the key elements in ultrafiltration and the force behind transport across the membrane is the compound's particle size (Nawaz *et al*., 2006). We will separate the compounds with molecular weights between 3000 Da and 100 KDa and above using this method. For the low molecular weight of polyphenolics, ultrafiltration with semi-permeable membranes is used for easy and rapid separation. UF technique is used to extract the polyphenols from Echinacea herb, grape seeds, and also from almond skins by the involvement of some membranes like polyether sulfone and regenerated cellulose (Prodanov *et al*., 2008).

Enzyme Assisted Extraction

Several enzymes, including pectinase, cellulase and gluconate are utilized in the extraction process to break down the polyphenols' cell wall complex (Meyer *et al*., 1998; Landbo and Meyer, 2001). There are benefits to using enzyme-assisted polyphenol extraction over traditional techniques. For example, Yu, Vasanthan and Temelli (2001) discovered a technique for pectinase that enhances the phenolics extraction from barley and apple pomace (Zheng *et al*., 2008; Yu *et al*., 2001).

Table 5: **Conditions for employing UMAE to extract phenolics from plant foods.**

Sample	Analyte	Solvent	Ultrasound power (W)	Microwave power (W)	UMAE time (s)	UMAE temperature (°C)	Solvent/ sample (mL/g)
Anoectochilus roxburghii	Quercetin	50% Ethanol	50	800	900	45	8
Arctium lappa	Caffeic acids	Ionic solution	50	400	30	--	20
Spatholobus suberectus	Flavonoids	70% Methanol	50	300	450	80	20
Tomato	Lycopene	Ethyl acetate	50	98	367	--	10. 6

Table 6: **SCWE conditions: phenolics extraction of plant-based materials.**

Species	Analyte	Temperature (°C)	Time (min)	Pressure (bar)	Solvent/ sample mL/g
Bitter melon	Phenolic compounds	130-200	10-120	--	--
Cinnamon bark	Phenolic compounds	150-200	60	60	--
Green tea	Catechin and epicatechin	140-260	--	38 -72	20
Oregano leaves	Phenolic compounds	25-200	15, 30	103. 4	--
Pomegranate seeds	Phenolic compounds	80-280	15 -120	60	10 -50
Potato peel	Phenolic compounds	100-240	30 -120	60	--
Rice bran	Phenolic compounds	125-200	5	20	2. 5
Terminalia chebula	Phenolic compounds	120-220	10 -150	40	--

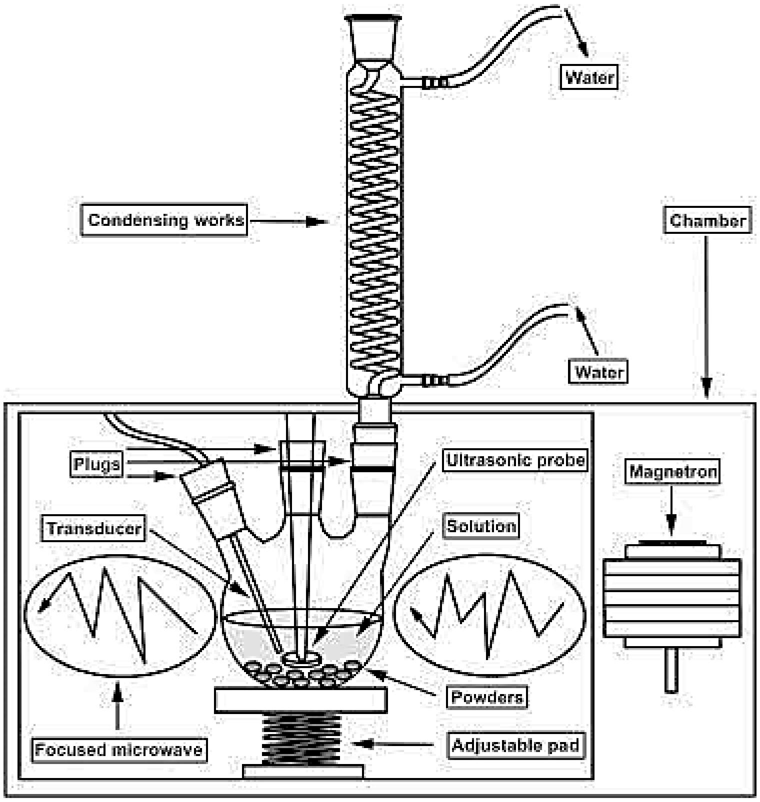

Figure 1: Device for extraction with ultrasonic-microwave assistance.

MODERN EXTRACTION TECHNIQUES

Ultrasound/Microwave Assisted Extraction (UMAE)

It is one of the new approaches to extract bioactive compounds using two potent radiation techniques i.e., microwave and ultrasound. In MAE, a dielectric mechanism was used to heat the sample to extract the bioactive compounds rapidly, whereas UAE makes the cavities into the sample by enhancing the solvent penetration capacity and mass transfer (Huie, 2002; Jiao and Zuo, 2009). This UMAE technique will reduce the extraction time, less solvent consumption and higher extraction yields than MAE and UAE methods (Rostagno *et al.*, 2010). The schematic representation of a hyphenated technique UMAE was shown in Figure 1.

UMAE technique used to extract phenolics from Burdock leaves by maceration, a phenolic yield of 9 mg/g was obtained (Lou *et al.*, 2010), whereas utilizing maceration alone produced a yield of less than 0. 5 mg/g. When compared to MAE, UAE, Soxhlet, and heated reflux extraction procedures, demonstrated that flavonoids are recovered from *Spatholobus suberectus* by UMAE, which achieved maximum yields in 7. 5 min by utilizing a 20 mL/g solvent-sample ratio (Cheng *et al.*, 2011). Table 5 displays the ideal conditions for polyphenols extraction using UMAE technique (Khoddmi *et al.*, 2013).

Subcritical Water Extraction (SCWE)

It is an Eco-friendly, quality and less time-consuming extraction technique for effective isolation of phenolic compounds (Kronholm *et al.*, 2007; Herrero *et al.*, 2006). When water turns subcritical temperature (about 100-347°C) at sufficient pressure, conserve it in liquid form, due to water collapse of intermolecular hydrogen bonds, water's dielectric constant can be reduced. The most effective way to extract phenolic compounds with significant amounts in industry without leaving any organic residues is by SCWE, which is intended for use as an antioxidant in food items (Miller and Hawthorne, 2000). Some developed methods for the extraction of polyphenols by using SCWE are shown in Table 6 (Khoddmi *et al.*, 2013).

High Hydrostatic Pressure Extraction (HHPE)

This is another cutting-edge method for isolating phenolics from plants utilizing non-thermal super-high hydraulic pressure (1000-8000 bar) which works on mass transfer phenomena (Zhang ShouQin *et al.*, 2005). Applying pressure increases a plant cell's permeability, which promotes mass transfer and cell diffusivity. The primary drawback of extraction methods like HHPE, SCWE and SCFE is high cost when compared with other extraction methods (Smith, 2002). HHPE can result in protein denaturation and cell deformation, which can lower the cell's selectivity and maximize extraction yield. It is employed to extract the polyphenols from cashew apple juice and green tea leaves (Queiroz *et al.*, 2010).

Table 7: GC conditions to detect phenolic compounds.

Sample	Derivatization	Phenolics Detected	Detection
Guarana	Derivatization with a mixture of hexamethyldisiloxane.	Quercetin; Benzoic acid; 3-Hydroxy benzoic acid; Gallic acid; Protocatechuic acid; Epicatechin.	GC-MS
Guava bagasse, Cabernet Sauvignon, Pinot Noir, and Isabella grape marcs wastes.	-----------	Succinic acid; azelaic acid; syringic acid; p-coumaric acid; gallic acid; ferulic acid; caffeic acid; epicatechin; quercetin; myricetin.	GC-MS
Cranberry	Dried phenolic extract derivatized with a mixture of N, O-Bis(trimethylsilyl) trifluoroacetamide and 1% trimethylchloro silane in pyridine.	Benzoic acid; o-, m-andp-hydroxybenzoic acid; p-hydroxy phenyl acetic acid; trans-cinnamic acid.	GC-MS
Saffron corms	Dried phenolic extract derivatized with a mixture of N-methyl-N-(trimethylsilyl)trifluoroacetamide, iodotrimethylsilane.	Acetic acid; o-phthalic acid; 2, 3-dihydroxy benzoic acid; catechin; epicatechin; vanillic acid; o-hydroxycinnamic acid; 2, 4-dihydroxy benzoic acid; p-coumaric acid; ferulic acid; caffeic acid; sinapic acid.	GC-MS
Mangosteen fruit	Dried phenolic extract derivatized with N, O-bis(trimethylsilyl) acetamide.	Hydroxybenzoic acid; protocatechuic acid; vanillic acid; caffeic acid; p-coumaric acid; ferulic acid; p-hydroxy phenylacetic acid;3, 4-dihydroxy mandelic; cinnamic acid.	GC-MS
Green tea	Derivatization with trimethyl sulfonium hydroxide.	Epigallocatechin; epicatechin; catechin; gallocatechin; kaempferol.	GC-MS
Various plant extracts	Dried phenolic extract derivatized with mixture of trimethyl chlorosilane and N, O-bis(trimethylsilyl)acetamide with dimethyldichlorosilane in toluene and dimethyldichlorosilane.	Gallic acid; p-hydroxybenzoic acid; gentisic acid; p-coumaric acid; vanillic acid; ferulic acid; syringic acid; catechin.	GC-MS

Other Methods of Extraction

A non-thermal method called the Pulsed Electric Field method (PEF) uses less energy to enhance mass transfer and cell membrane lyses (Puertolas *et al.*, 2012). It will minimize the quality of deterioration of food products, mainly bioactive compounds. In PEF, the highest yield of phenolics will be observed in chardonnay grapes, merlot grapes, red cabbage, strawberry, and tempranillo grapes (Kannan, 2011; Odriozola-Serrano *et al.*, 2008; Lopez *et al.*, 2008). A popular method for isolating phenolics from plant materials is called "Accelerated Solvent Extraction, " or "ASE. " It involves utilizing organic solvents in an inert atmosphere at high pressure and temperature. Under these circumstances, the solvent enters the plant cells fast and preventing the phenolics from degradation (Wibisono *et al.*, 2009).

Phenolics: Purification and Fractionation

Different types of contaminants and interfering substances may be present in extracts of phenolics and should be removed before the identification and quantification. Phenolic compound extracts can be concentrated using vacuum, and petroleum ether or diethyl ether can be used to remove lipids and other undesirable components (Naczk and Shahidi, 2006). Neutral organic solvents are used to prevent the loss of labile acyl and/or sugar residues in some types of phenolic compounds, such as anthocyanins, where high concentrations may produce these effects (Antolovich *et al.*, 2000). Solid-phase or liquid-liquid phase extraction procedures are typically used to purify and fractionate phenolics.

Solid Phase Purification/Extraction (SPE)

It is a commonly employed method for the separation, refinement, and initial concentration of phytochemicals, particularly those phenolics. Alkylated silica gels, primarily C8 and C18, are the sorbents most frequently utilized for their superior separation and selectivity. Additionally, two cartridge combinations with various sorbents (C18 and quaternary amine) and polymeric solvents were also used for the extraction of phenolic compounds (Klejdus and Kuban, 2000; Ziakova and Brandsteterova, 2002). Compared to liquid-liquid extraction, the SPE technique yields full extracts (cleaner extracts) and is faster and more reproducible. Ion exchange columns in conjunction with the SPE method are occasionally employed to isolate phytochemicals. Solid-Phase

Micro Extraction (SPME), a new technique was developed by scientists for sample extraction and purification which is rapid, inexpensive and free from solvent. Researchers employ sorbent coated silica fibers, which are often immersed to extract the analytes in aqueous media. The fibers are then transferred directly for additional chromatographic analysis, where the samples are ultimately separated and examined. Phenolic compounds analysis uses two main coated fibers, such as polydimethylsiloxane and polyacrylate. The primary drawback of the technique is its inability to process a high amount of samples (Vinas *et al*., 2009).

Liquid-Liquid phase Extraction (LLE)

It is also one of the most effective technique for phenolic compound purification/extraction of plant extracts. The plant material was steeped in boiling water, allowed to cool for 12 to 24 hr, and then the filtered plant extract was concentrated at a lower pressure and temperature in accordance with the nature of phenolic chemicals. The concentrated extract was washed with water to remove precipitated resins followed by treating with petroleum ether to remove the fatty material. The ethereal layer underwent treatment with 5% Na_2CO_3 to convert the phenolic acids into their sodium salts that are soluble in water. Acidify the alkaline layer with dil. HCl and extract again with diethyl ether. To eliminate acid and water from the resulting ether extract, it was carefully rinsed with water. Phenolics are separated with this extraction method primarily by partitioning between two immiscible liquids; these mobile phases often function as a miscible auxiliary solvent. Compared to SPE, this approach has a number of drawbacks, including the necessity for evaporation stages to remove surplus solvents and the enormous quantities of solvents it consumes. It also requires a significant amount of time and labor. Compared to other techniques like SPE, the main benefit of this technology was its capacity to handle a huge number of samples (Degenhardt *et al*., 2000).

Quantification of Phenolics

It is difficult to quantify phenolics, because it depends on the type of phenolic group present in the molecule. Although, methods like spectrophotometry, HPLC, GC and LC/GC-MS are frequently used to quantify the phenolics (Liu *et al*., 2008; Naczk and Shahidi, 2004).

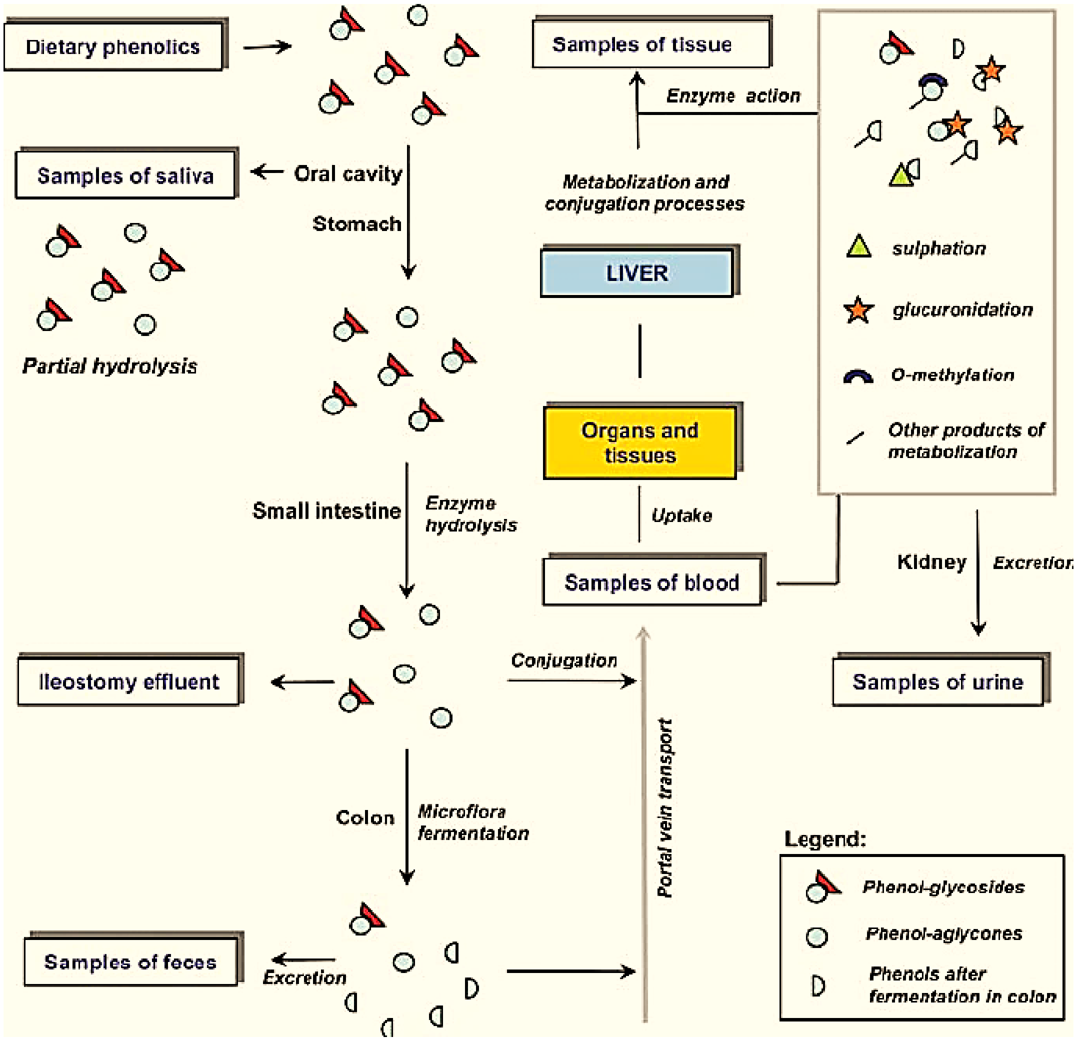

Figure 2: Diagram showing the resorption, metabolism and excretion of plant phenolics in mammals.

Assays by Spectrophotometry

Spectrophotometry is a simple technique used to quantify plant phenolics by two methods Folin-Denis and Folin-Ciocalteu depends on the chemical reduction in the presence of reagents like tungsten and molybdenum (Naczk and Shahidi, 2006; Stalikas, 2007). To quantify total flavonoids present in alcoholic extracts which have phenolic hydroxyl group(s) in the range of 410-423 nm using $AlCl_3$ as reagent (Fernandes *et al.*, 2012). Using methylcellulose, researchers developed a technique to measure proanthocyanidins in grape extract (Sarneckis *et al.*, 2006). Dai *et al.*, reviewed various methods used to evaluate hydrolysable tannins (Dai and Mumper, 2010; Hartzfeld *et al.*, 2002). Anthocyanins are measured in the wavelength range of 490-550 nm by spectrophotometry in weak acidic media (Giusti and Wrolstad, 2003). Because they are straightforward and affordable, calorimetric methods used to measure phenolics; however, they only provide an estimate of concentrations over a specific minimum threshold quantify only. These methods can be helpful for quickly and affordably screening a large number of samples (Ignat *et al.*, 2011).

Gas Chromatography

An additional method used to isolate, identify, and quantify phenolic substances such flavonoids, tannins, and phenolic acids is Gas Chromatography (GC). The derivatization and volatility of phenolics is the major concern for GC and it's not applicable to HPLC method (Smolarz, 2001). Silyl derivatization is the best method among different methods of derivatization to quantify the phenolic compounds. Shadkami *et al.*, (2009) and Robbins (2003) developed a method to quantify the phenols using most common fused silica capillary columns by GC technique (Shadkami *et al.*, 2009). The most used detector for phenolics is the Flame Ionization Detector (FID), while Mass Spectrometry (MS) has lately gained popularity (Robbins, 2003). The difficulties of evaluation of flavonoid glycosides were solved by using GC-MS with high resolution at high temperature. Therefore, GC-MS analysis is more proficient than HPLC for phenolic and flavonoid analysis since it offers quicker analysis, good resolution and baseline separation (Ignat *et al.*, 2011; dos Santos Pereira *et al.*, 2004). Some of the quantified polyphenols by using GC technique is shown in Table 7 (Khoddami *et al.*, 2013).

High Performance Liquid Chromatography (HPLC)

To isolate and quantify polyphenolics, HPLC is the most efficient method (Naczk and Shahidi, 2004). To quantify purified phenolics, RP-HPLC-Photodiode Array Detector (PDA) at wavelength range of 190-380 nm is used. Pre-concentration from complicated matrices is the sole basis for the phenolics' sensitivity and detection (Ignat, 2011). The choice of column and its temperature and running time are crucial factors in the identification of phenolics (Robbins, 2003; Reichelt *et al.*, 2010; Roggero *et al.*, 1997). Phenolics are generally detected using UV-Vis and Photodiode Array (PDA) detectors (Roodman *et al.*, 2010). HPLC-MS with various ionization techniques are useful for structural characterization, improving sensitivity and specificity of various phenolics (Oh *et al.*, 2008; Amaral *et al.*, 2012; Zhang *et al.*, 2010; Lee *et al.*, 2008; Edenharder *et al.*, 2001; Bianco *et al.*, 2001). New methods for analyzing phenolic compounds are named HILIC (Hydrophilic Interaction Liquid Chromatography) and 2-D LC (2-Dimensional Liquid Chromatography), which are more popular because of their excellent compatibility and increased accuracy when combined with MS (Jandera, 2008).

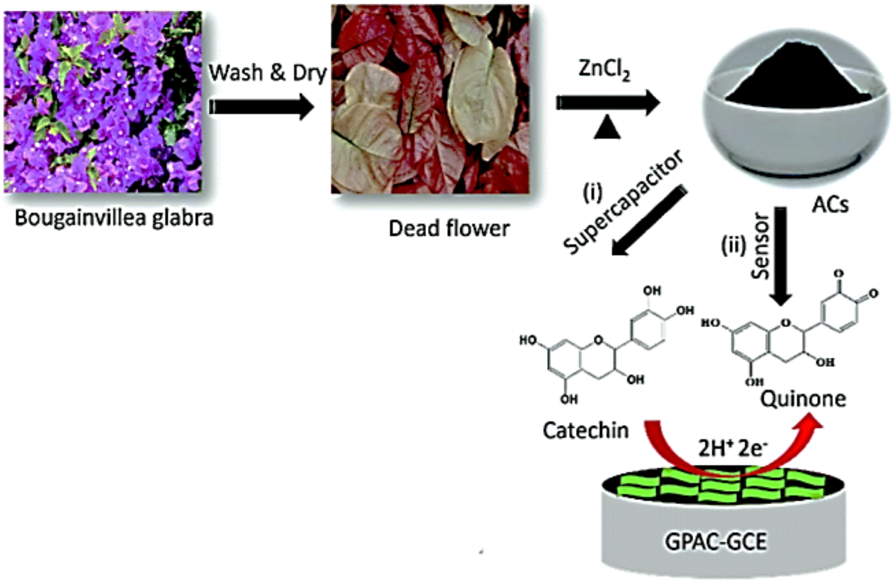

Figure 3: Creation of Activated Carbon (GPAC) that resembles a graphene sheet and its use as an electrode material for catechin detection.

Other techniques for separation and quantification of phenolics

To separate the phenolics from food materials, two partitioning techniques are employed known as Paper Chromatography (PC) and Thin-Layer Chromatography (TLC). Compared to HPLC and GC, PC is a simpler method that is used to a lesser degree (Naczk and Shahidi, 2006). A powerful technique is TLC especially for crude plant extracts than PC to analyse phenolics (Ignat, 2011). The widespread and exclusive technique used to separate and purify various polyphenolics called as High-Speed Counter Current Chromatography (HSCCC) works on the basis of biphasic liquid-liquid partitioning principle (Naczk and Shahidi, 2004; Cao *et al*., 2009; Wang *et al*., 2010). A high-resolution technique applied for qualitative analysis of polyphenolics such as Capillary Electrophoresis (CE) for low charged, medium-molecular-weight, low volume of samples. Other most widely used techniques for analysis of phenolics are Micellar Electro Kinetic Chromatography (MEKC), Capillary Electro Chromatography (CEC) and Capillary Zone Electrophoresis (CZE) coupled with UV, electrochemical or MS detectors among the different types of CE separation techniques were also applicable (Rybarczyk *et al*., 2008). Moreover, researchers are using HPLC methods like 2-D LC and HILIC to simultaneously identify phenolics with a variety of polarity (Sun *et al*., 2012).

Metabolism of phenols in human body

After being consumed as food, the polyphenols are absorbed in the digestive system and go through a chemical transformation there. The exact chemical transformation of polyphenols in the oral cavity has not yet been determined because salivary enzymes can contribute to the hydrolysis of glycosides to some extent (Ice and Wender, 1952; Patil *et al*., 2009; Unger, 2009). The primary step in the digestion of polyphenols is called deglycosylation, and it is carried out by intestinal enzymes such as cytosolic β-glucosidases and lactase-phlorizin hydrolyase (Manach *et al*., 2004; Day *et al*., 1998). Phenols are processed in various tissues after being absorbed in the digestive tract, with the components that are not absorbed being eliminated. This process involves the conjugation of glucuronic acid with phenols in the intestinal mucosa, followed by conjugation reactions in the liver (Saude and Sykes, 2007). Figure 2 shows a schematic representation of how plant phenolics are reabsorbed, metabolized, and excreted by mammals.

Electrochemical Methods for Quantification of Phenols

Plant phenolics can be analyzed by electrochemical detection by utilizing their charge and electrochemical characteristics. These electrochemical methods are divided into following types:

Potential analysis

In potential analysis, electrode potential and concentration can be able to find out the concentration of polyphenols present in the solution or media.

Voltammetry and Polarograph

A special kind of electrochemical analysis called volt-ampere and polarography can create an electrolytic cell by using a working and reference electrode.

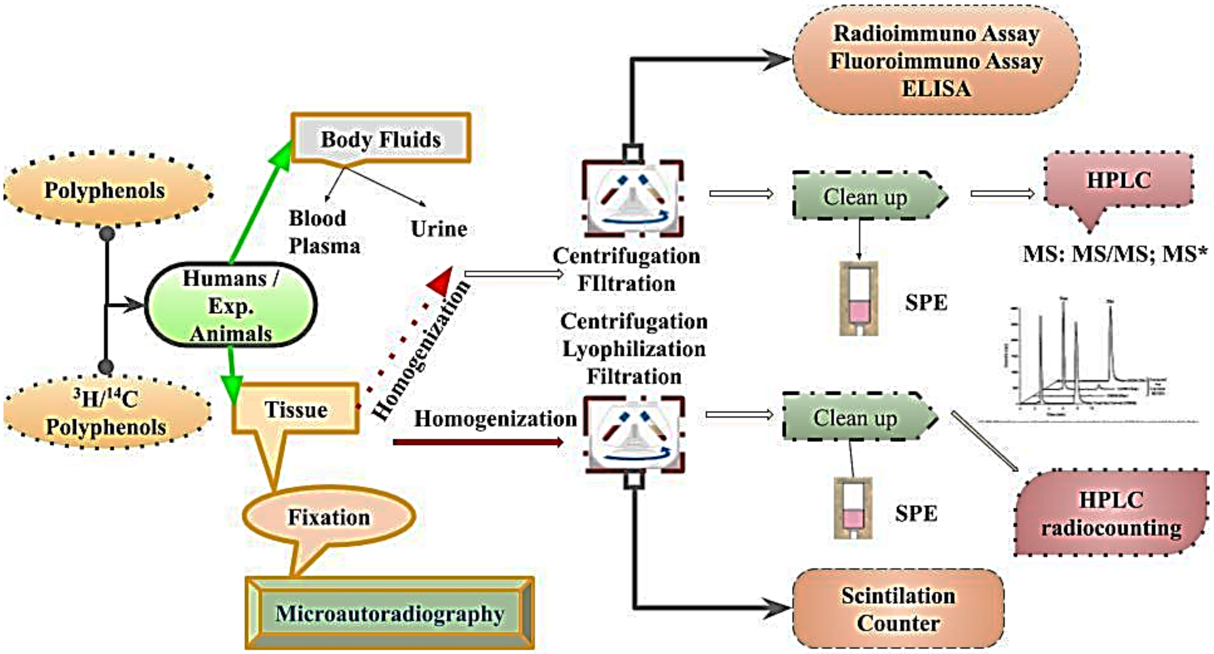

Figure 4: An experimental concept for plant phenolics detection in clinical samples.

Electrolysis and Coulomb analysis

These are the first electrochemical techniques for polyphenol analysis that have been found. New electrode materials have been developed recently for improving detection sensitivity. Catechins are determined with various electrochemical biosensors have been developed such as gold-nanoparticles-polypyrrole composite (Singh *et al.*, 2013), laccase immobilized on gold-nanoparticles encapsulating a dendrimer bound to a conductive polymer catechin sensor (Rahman *et al.*, 2008) and lignocellulosic biomass-derived, Graphene sheet-like Porous Activated Carbon (GPAC) sensor (Figure 3) (Yang *et al.*, 2009).

The majority of applications for gallic acid is in the food, biological, medical and chemical industries and determined electrochemically using SiO_2 Natural Phosphate (NP)-modified carbon paste electrodes (Tashkhourian and Nami-Ana, 2015). These SiO_2 NPs' large specific surface area and superior accumulation efficiency greatly increase the gallic acid current signal. For example, a multi-walled carbon nanotube-modified carbon paste electrode used to determine the gallic acid (Ganesh *et al.*, 2019). These modified electrochemical sensors can detect in the range of 1-33. 75 µM of polyphenolics (Zhou *et al.*, 2019).

Examination of plant polyphenolics in medicinal specimens

In clinical samples, polyphenols identification is usually carried out in plasma or urine and will get the most valuable information on their metabolic reactions. The sample variability should be taken into account while creating a new technique for the analysis of metabolites in urine or plasma since the quality and quantity of the consumed sample can significantly affect the composition of urine.

Sample preparation and hydrolysis

Generally, in polyphenol analysis two approaches are used. One approach is the examination of total polyphenolic content in homogenates to eliminate the conjugated forms formed by enzymatic or chemical hydrolysis (Wang and Morris, 2005). After that, the sample is dissolved in an appropriate solvent to liberate the bound proteins' total polyphenols. The second approach doesn't involve hydrolysis or deproteinization; instead, it looks at the free polyphenols or their conjugates. In the end, a clean-up SPE process is used to purify polyphenolic samples that have been hydrolyzed or not. Ascorbic acid or some other reducing agents are added to the samples to prevent the oxidation (Abd El Mohsen *et al.*, 2002). Various methods for preparing samples and hydrolysis of polyphenols are demonstrated in Figure 4.

Techniques for analysis of phenolics in urine and plasma

There are several ways to analyze plant phenols; the most widely used ones are RP-HPLC-UV-Vis-DAD, ESI-MS, electrochemical, and NMR analysers (Tang *et al.*, 2009). The absorption, metabolization and excretion of a wide range of phenols are frequently used to investigate the pharmacokinetic characteristics. HPLC combined with a UV-Vis detector was utilized to analyze the phenolic acids, caffeic acid, and chlorogenic acid found in the urine and effluents of healthy male and female ileostomy patients (Olthof *et al.*, 2001). A validated HPLC-UV-Vis-DAD method was established for the intravenous application of *Ginkgo biloba* extract to analyze flavonoids and other associated compounds in rat plasma (Klejdus *et al.*, 2008).

Techniques for measuring polyphenolics absorption in tissue

Micro autoradiography was employed to analyze the distribution of radioactively tagged polyphenols (i.e., ^{1}H or ^{13}C) in fixed tissue. In other studies, when the tissue is homogenized, the extracts obtained by autoradiography are used to quantify the polyphenols. A technique for polyphenol analysis that does not require radioactive chemical labeling is created (Mohsen *et al.*, 2002).

CONCLUSION

Polyphenols exhibited broad spectrum of biological activities and a critical function in enhancing human health and lowering the risk of disease, these are considered as a feasible green resource and an important secondary metabolite in plants. These benefits of polyphenols lead to an increased interest in researchers to develop simple and rapid methods for the polyphenols. This review discusses the extraction, separation and purification, quantification, metabolism and analysis of polyphenols in clinical samples and also provides information about the modern extraction techniques for the identification of polyphenols.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

ABBREVIATIONS

UV-Vis: Ultraviolet-visible Spectroscopy; **NIR:** Near Infra-Red; **DAD:** Diode Array Detector; **UF:** Ultra Filtration; **ESI:** Electron Spray Ionization; **DPV:** Differential Pulse Voltammetry; **CV:** Cyclic Voltammetry; **HCl:** Hydrochloric Acid; **NaOH:** Sodium Hydroxide; **N_2:** Nitrogen; **SO_2:** Sulphur dioxide; **CO_2:** Carbon dioxide; **Na_2CO_3:** Sodium bicarbonate; **$AlCl_3$:** Aluminium chloride; **He:** Helium; **ACN:** Acetonitrile; **SiO_2:** Silicon dioxide; **KI:** Potassium Iodide; **W:** Watt.

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