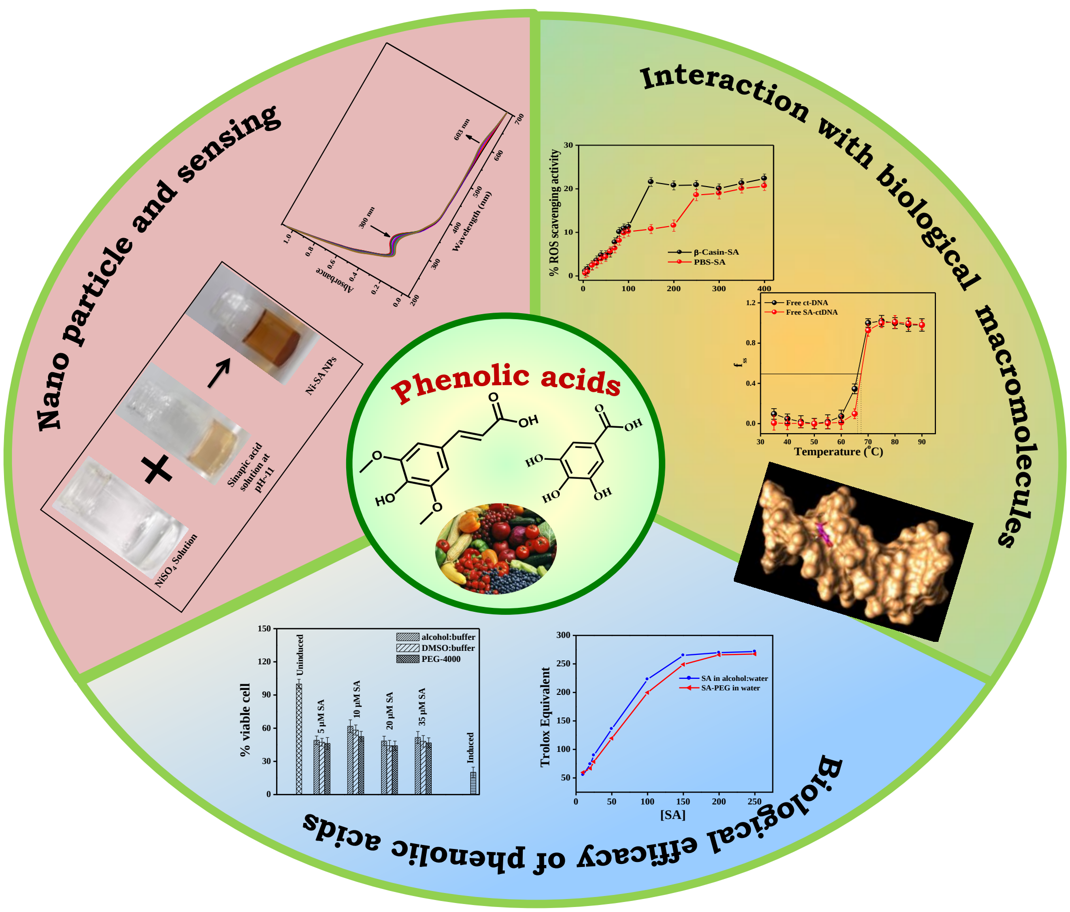
Chapter 1

Introduction



Modern medicine has gained popularity among people due to its accuracy and efficiency. But people are also concerned about the side effect of modern drug and hence they are looking for natural product not only for their remedies but also for nutritional requirements. In ancient times people used herbal remedies for the treatment of variety of chronic and infectious disorders. The knowledge of the therapeutic potential of these herbal remedies is learned from their experience and they passed this information down through the generations [Santic et al., 2017]. Therefore people are now turning into herbal medicines for their safety as well as minimal side effects [Sudheesh et al., 2018]. The majority of people in developing nations use herbal medicines and phytonutrients on a regular basis due to their spiritual and cultural perspectives, as well as the expensive cost of modern treatments. In the last few decades, the study of medicinal plants is taken seriously, and extensive research is being going on due to their wide variety of therapeutic potential such as antioxidant, antifungal, anti-inflammatory, anticancer, antiperoxidative, antibacterial, hypoglycemic, hypolipidemic etc. [Mondal et al. 2021]. Besides, in modern days people are not only taking food to compensate their hunger, but are also concerned with the nutritional values of the foods. In this virtue, addition of these plant-derived components with high spectrum of bioactivities in food industries is a topic of discussion.

1.1. Plant secondary metabolites

The term secondary metabolites are the organic molecules that are produced in the living plant cells and are not directly involved in the growth, development, reproduction or other primary functions of the plants but are involved in the biological activity on the human health. However, secondary metabolites are frequently protecting plants against biotic or abiotic stresses. They are also essential for communication in both antagonistic interactions, such as disease, and mutualistic partnerships, such as pollination and legume root nodules [Chomel et al., 2016]. Secondary metabolites can be categorized according to their composition (containing nitrogen or not) and chemical structure (such as having rings or containing sugar) [Isah, 2019]. The four major classes are; terpenoids, phenolic compounds, nitrogen containing compounds, which are further categorized into other subclasses as shown in Fig. 1.1.

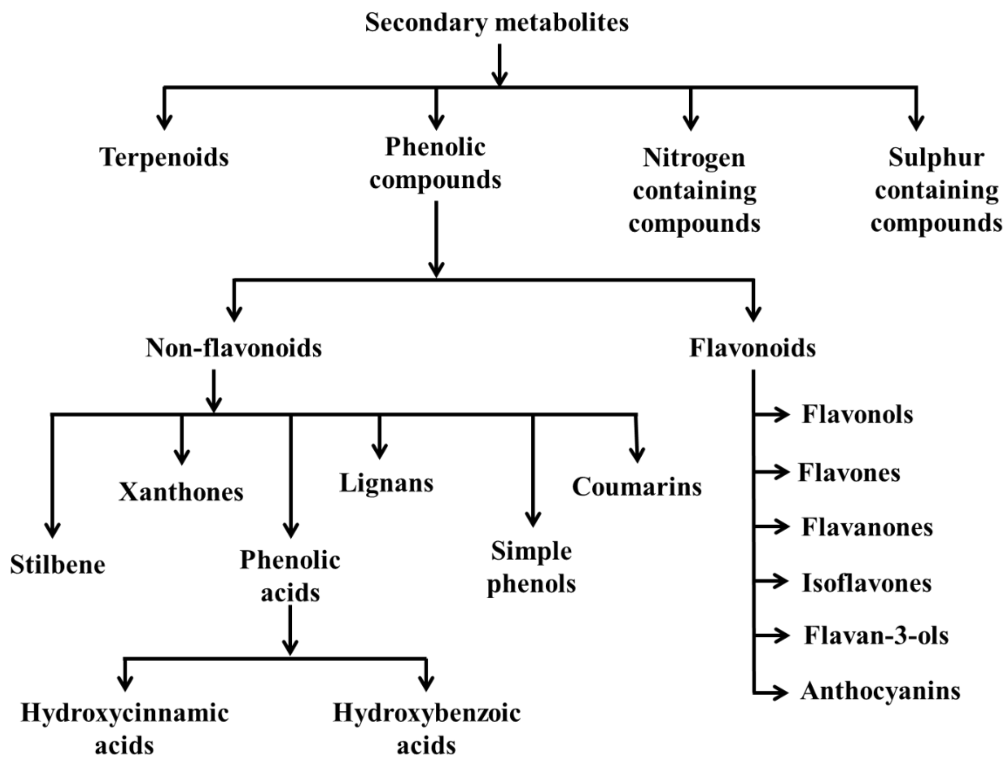


Figure 1.1. Classification of secondary metabolites

Phenolic compounds (PCs) are one of the most common classes of secondary metabolites in plants found in nature and divided mainly into flavonoids and non-flavonoids (cf. Fig. 1.2). Numerous investigations have revealed that, due to the huge antioxidant potential of phenolic compounds, it has played significant role in human diet, it not only maintains the quality of the food but also lowers the risk of contracting certain diseases [Minatel et al., 2017]. According to studies, eating a diet rich in phenolic compounds helps to slow down the ageing process and reduces the risk of oxidative stress and inflammation that are linked to chronic diseases like cardiovascular disease, cancer, arteriosclerosis, diabetes, cataract, and diseases of the nervous system and cognitive functions [Tanaka et al., 2012; Pojer et al., 2013].

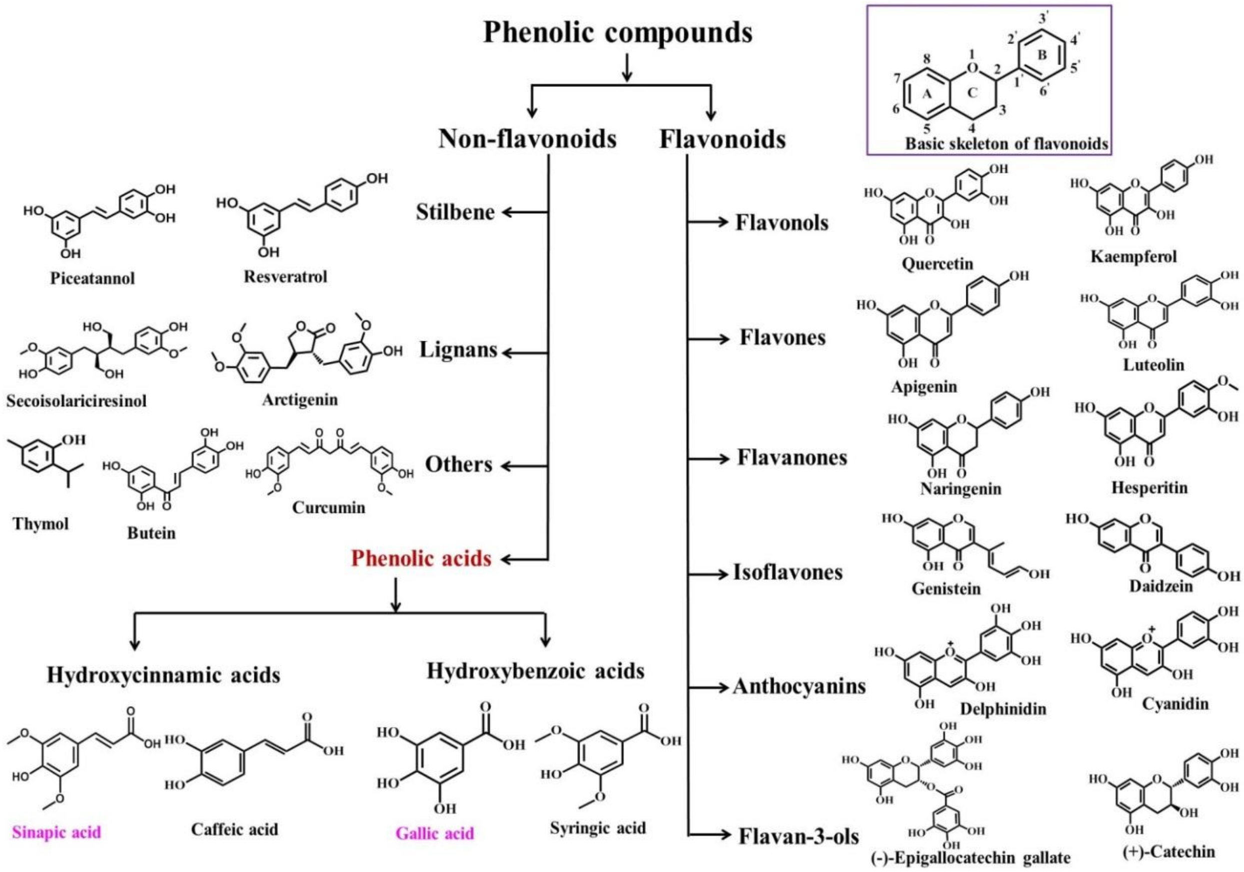


Figure 1.2. Classification of phenolic compounds with few well-known examples

1.1.1. Flavonoids

Flavonoids are the most abundant type of plant phenolic compounds. They include almost 6000 of the over 8000 phenolic compounds that are present in plant food [Vuolo et al., 2019]. Flavonoids are low molecular weight compounds, composed of two aromatic rings (A and B rings) joined by an oxygen heterocyclic ring (C ring) and contain 15 carbon atoms, arranged as C6-C3-C6 configuration [Lafay et al., 2008]. Depending on the variation pattern of the hydroxyl groups and heterocycle rings, flavonoids are further divided into flavonols, flavones, flavanones, isoflavones, flavan-3-ols or catechins, and anthocyanins [Brodowska, 2017].

1.1.2. Non-flavonoids

The well-known non-flavonoids compounds found in the human diet are phenolic acids, stilbenes, lignans, etc. [Vuolo et al., 2019].

Phenolic acids (PAs): Phenolic acids are organic compounds that have at least one aromatic ring with at least one hydrogen replaced by a hydroxyl group [Vuolo et al., 2019; Heleno et al., 2015]. They are divided into two groups, viz., hydroxybenzoic acids (HBAs) and hydroxycinnamic acids (HCAs) that are originated from non-phenolic compound like benzoic acid and cinnamic acid, respectively [Williamson, 2017].

HBAs generally have the formula C6-C1 (cf. Fig. 1.2), however they can differ from this basic structure in certain ways, such as by hydroxylating and methoxylating of the aromatic rings. Some of the common HBAs are 4-hydroxybenzoic acid, salicylic acid, protocatechuic acid, syringic acid, gentisic acid, gallic acid, vanillic acid, ellagic acid, and hexahydroxydiphenic acid (ellagic acid dilactone). Fruits, vegetables, teas, and grains are the main nutritional sources of these substances [Clifford et al., 2000].

HCAs have a fundamental structure of C6-C3 (cf. Fig. 1.2) with a double bond in the side chain that can be in either a cis or a trans configuration. They typically appear in food as monomers, dimers, or polymers; they can condense with alcohols, hydroxy acids, or mono- or disaccharides to produce esters; or they can condense with amines to form amides. Although they are rarely seen in their natural state, however some processed foods can have free forms as a result of the freezing, fermenting, or sterilising procedures [Rommel et al., 1993]. Some of the common HCAs are coumaric acid, ferulic acid, sinapic acid, caffeic acid. Fruits such as apples, cherries, different berries, peaches, plums, and some citrus fruits are the primary dietary sources of HCAs [Mattila et al., 2005; D'Archivio et al., 2007].

Studies on phenolic compounds is now gaining popularity due to their diverse biological properties, which include antioxidant, antibacterial, anticancer, antidiabetic, antiinflammatory, antiviral, antiobesity, blood lipid-lowering actions, and many more [Ruel et al., 2007; Saibabu et al., 2015]. PCs are powerful antioxidants as well as radical scavengers. They are chemicals that protect biomolecules (proteins, nucleic acids, polyunsaturated lipids, and carbohydrates) against oxidative damage caused by free radicals (such as hydroxyl radical ($^{\bullet}OH$), superoxide radical

($O_2^{\bullet -}$), nitric oxide radical ($NO^{\bullet}$), alkoxyl radical ($RO^{\bullet}$), etc.) and also have anti-inflammatory, antidiabetic, cardioprotective, neuroprotective, anticancer, and antiaging activities [Heleno et al., 2015; Zhang et al., 2017].

The structure-activity relationship of PCs determines their antioxidant activity, which includes the number and locations of the hydroxyl group (-OH), the existence of a double bond (C2=C3), glycosylation, and the presence of substituents in the rings [Bendary et al., 2013; Wang et al., 2018; Rodriguez-Arce et al., 2021]. The primary antioxidant properties of PCs, are accomplished through two basic mechanisms: free radical inactivation or hydrogen atom transfer (HAT, equation 1.1) and single electron transfer (SET, equation 1.2). In the first process the free radical ($R^{\bullet}$) is removed by a hydrogen atom from the antioxidant (ArOH) with the formation of $ArO^{\bullet}$ radical. The higher antioxidant activity of the antioxidant (ArOH) depends on the bond dissociation energy (BDE) of the O-H of the antioxidant (ArOH). Hence lower the BDE higher is antioxidant activity.

$$\mathbf{ArOH + R^{\bullet} \longrightarrow RH + ArO^{\bullet}} \qquad (1.1)$$

In the second mechanism, the antioxidant (ArOH) can donate a single electron to the free radical forming the radical cation ($ArOH^{\bullet +}$). In this case lower the ionization potential (IP) of the antioxidant (ArOH), easier is the electron transfer, indicating greater antioxidant activity.

$$\mathbf{ArOH + R^{\bullet} \longrightarrow R^{-} + ArOH^{\bullet +}} \qquad (1.2)$$

Deoxyribonucleic acid (DNA) damage is triggered by a variety of factors, including both external (e.g., ionizing radiation, UV light, and certain chemicals), and endogenous [e.g., reactive oxygen species (ROS), replication stress] agents. Oxidative stress is one of the main sources of DNA damage, which are brought on by an excess of ROS [Martins et al., 2021; Whitaker et al., 2017]. This DNA damage causes various types of cancer including breast, colon, ovary, lung, etc [Yang et al., 2009]. Many studies revealed that the PCs have the protective activity of DNA damage and stop tumor cells from progressing [Weng et al., 2012]. The protective activities of phenolic acids like, sinapic acid, caffic acid, protocatechuic acid, gallic acids are well reported [Ho et al., 2010; Lodovici et al., 2001; Silva et al., 2012]. Recent studies have proposed several PCs as natural antiviral treatments for coronavirus illness (COVID-19)

[Augusti et al., 2021; Ibrahim et al., 2021; Huynh et al., 2020; Zia et al., 2021; Orfali et al., 2021].

1.1.3. Applications of Phenolic compounds

PCs have a variety of biological uses in several industries because of their many functional characteristics (Fig. 1.3). Few of them are discussed below:

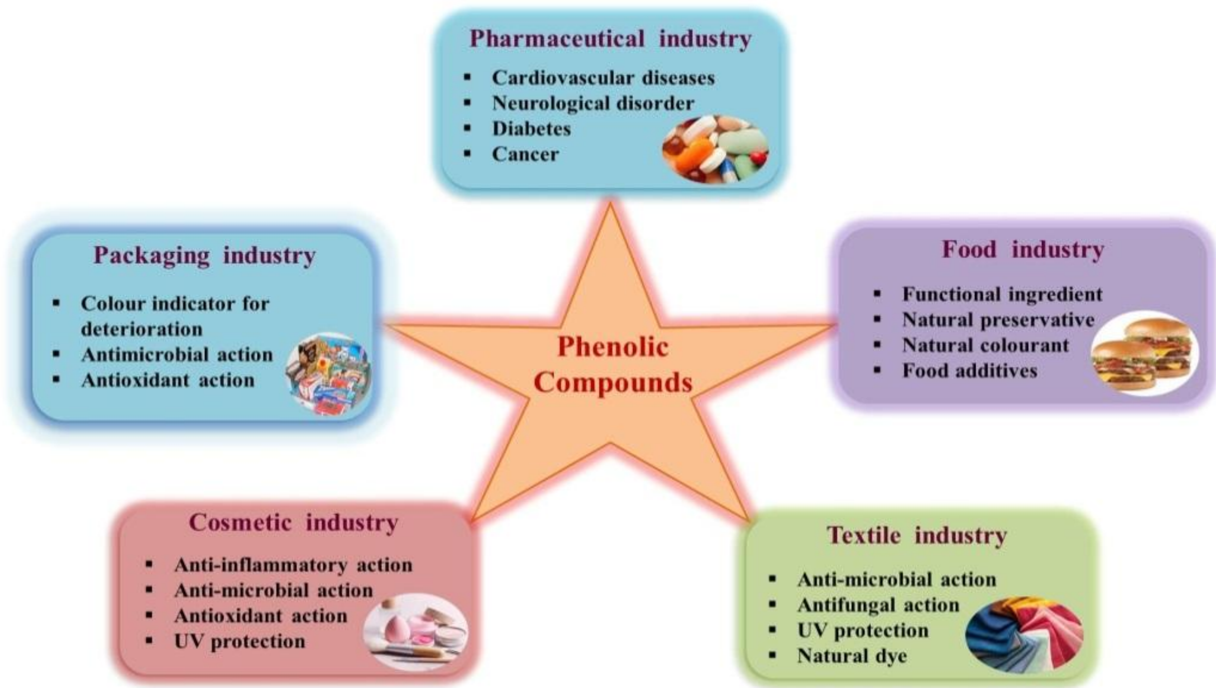


Figure 1.3. Application of PCs

Food industry: Antioxidant and antibacterial properties of PCs plays an essential role in the use of these substances as preservatives and extending the shelf-life of a variety of foods [Albuquerque et al., 2021]. The oxidative stability of oil increases by adding various PC-rich extracts/herbs such as olive leaf extract, rosemary extract, oregano [Albuquerque et al., 2021]. They have been also utilised to improve the food's organoleptic (flavour, astringency, and hardness), colour, sensory attributes [Kumar et al., 2019]. For instance, anthocyanins is a well-known food coloring additives which is allowed by the European Food Safety Authority (EFSA) under code E163 [Albuquerque et al., 2021] in food industry.

Cosmetic industry: The applications of natural PCs in cosmetic industries have mainly been associated with antiaging, antimicrobial, anti-inflammatory, and anticancer activities. PCs can protect the ultraviolet (UV) radiation due to presence of chromophores in it [Albuquerque et al., 2021]. Some of the PCs like quercetin, resveratrol and hydroxycinnamic acids shows well-known sun protection factor (SPF) and prevent the penetration of solar radiation into the skin.

Packaging industry: Functional food packaging can be used in place of synthetic packaging because of its ability to minimise moisture loss as well as its antioxidant and antibacterial properties [Wang et al., 2019]. Anthocyanins have the potential to serve as natural acid-base indicators in food packaging since anthocyanins can exhibit different colors at different pH (red at pH ∼2 and green pH ∼11) [Albuquerque et al., 2021]. The other PCs, namely gallic and caffeic acids, shows antibacterial activity against Bacillus subtilis and Staphylococcus aureus [Albuquerque et al., 2021].

Pharmaceutical industry: The PCs have numerous biological functions, including antioxidant, anti-inflammatory, and antibacterial effects etc [Albuquerque et al., 2021]. Because of these biological features, PCs can help to prevent and treat a variety of illnesses and diseases, including cardiovascular disease, cancer, Alzheimer's, diabetes, and hypertension etc [Shahid et al., 2013; Perumal et al., 2009]. As a result, they can be utilized as therapeutic agents in the pharmaceutical business. PCs, like kaempferol, naringin and anthocyanins have the ability to inhibit the growth of different tumours activity on melanoma, oesophageal and breast carcinomas, respectively [Kim et al., 2016; Su et al., 2018; Tajaldini et al 2020].

1.2. Interaction of Phenolic compounds with biological macromolecule

The interaction between the small naturally occurring bioactive molecules like PCs and biological macromolecules like serum albumin and DNA under physiological pH is one of the most important topics in recent days [Sengupta et al., 2019]. Because these bioactive compounds directly affect the biological function of the living organism.

Serum albumin is the most abundant protein found in blood plasma and has a great ability to bind with PCs. It also plays an important role to transport and disposition of various exogenous and endogenous compounds at target sites [Sengupta et al., 2019].

Deoxyribonucleic acid (DNA) is another biological macromolecule that carries genetic information for the development and functioning of an organism. DNA is made up of two biopolymer strands that are coiled around each other to form a double helix. These two biopolymers are formed by polymeric addition of the simpler units of nitrogen-containing nucleobase, adenine (A), thymine (T), guanine (G) or cytosine (C) also called polynucleotides. The region where the two strands are close to each other (deep-narrow) is known as minor grove, whereas the region where they are far apart (shallow-wide) is known as major groove [Shi et al., 2015]. Small molecules attached to DNA, may change or prevent the function of DNA. Therefore it is not only important to understand the mechanism of interaction but also provide beneficial knowledge for the improvement of new therapeutic drug designing. Hence, the interaction study of small molecules with DNA has become a current issue in the area of chemistry, life sciences, as well as medicine [Shi et al., 2015; Sun et al., 2014]. Generally, small molecules bind to DNA via non-covalent interactions. The mode of non-covalent interaction between small molecules and DNA is further classified into three different types: groove binding, intercalation, and external binding (electrostatic binding) [Sarkar et al., 2008].

- <u>Groove binding,</u> where the small molecule can bind the deep major or shallow minor groove of the DNA helix via van der Waals interaction and hydrogen bonding interaction [Sirajuddin et al., 2013].
- <u>Intercalation,</u> where small molecules stack between adjacent DNA base pairs and produce a considerable amount of p-electron overlap without forming covalent bonds and breaking up the hydrogen bonding interactions between the DNA base pairs. DNA intercalators are stabilized through π-π stacking interaction. DNA intercalators are used to prevent DNA replication in cancer cells that are growing quickly, hence used in chemotherapeutic treatment [Hegde et al., 2012].
- <u>External binding,</u> it is also known as electrostatic binding. This type of binding occurs when cationic molecules are forming non-specific interaction i.e. outside edge stacking interaction with the negative phosphate backbone of DNA [Sarkar et al., 2008].

1.3. Bioavailability of Phenolic compounds

Recently, researches based on uses of PCs have sparked a lot of interest in the functional food industry due to their potential on human health benefits. But, the fundamental drawback of PCs is their limited bioactivity, which is mostly brought about by their poor stability, low water solubility, and restricted membrane permeability [Chen et al., 2019].

Thus, the scientific communities have been resorted to a number of chemical and physical techniques such as nanoparticle formation, encapsulation, glycosylation, metal complexation, co-encapsulation, etc., to deal with such issues [Ahmad et al., 2022; Bisht et al., 2007; Li et al., 2005; Ma et al., 2007]. Among the mentioned approaches, nanoparticle formation and encapsulation are widely applied techniques adapted by the scientific community that can improve the stability, bioavailability, and bio-efficacy of PCs by protecting them from environmental stress, improving retention time, and controlling release at target sites [Ezhilarasi et al., 2013; Xiao et al., 2017]. In the following section, some of the well-utilized techniques are discussed in brief.

1.3.1. Nanoparticle formation

Nanoparticles have their special characteristics such as high surface to volume ratio, ultra-small sized dimensions, facile penetration and absorption, and bioactivity augmentation [Ahmad et al., 2022]. Thus, their applications as carrier system for PCs are being researched extensively nowadays [Kaviyarasu et al., 2012; Brigger 2012]. Tuning the surface of nanoparticles for a potential therapeutic impact involves the use of targeting probes, such as particular antibodies, ligands, antigenic agents, etc. Some well-known examples of nanoparticles are silver nanoparticles, gold nanoparticles, nickel oxide nanoparticles, iron oxide nanoparticles, mesoporous silica nanoparticles (MSNs), carbon quantum dot (CQD), carbon nanotube (CNT), etc. [Ahmad et al., 2022; Barui et al., 2020].

1.3.2. Encapsulating systems

Some examples of encapsulating systems are:

i. Micelles: Micellar systems have great features in industrial and food applications due to formation of thermodynamically stable mixtures of polar and non-polar solvents to solubilize hydrophobic food-related substances such as PCs or all types of preservatives [Cid et al., 2019]. Among various miceller systems, milk proteins are most popular due to their least toxicity [Welch et al., 2021]. β-casein (β-CN) are natural carriers that carry micronutrients; amino acids; etc. and can bind a variety of PCs, resulting to increase the bio-efficacy as well as stability of the PCs [Livney, 2010].

ii. Liposomes: A phospholipid-based membrane encloses an aqueous inner core in a liposome; where hydrophobic drugs can be remain in lipid bilayers and hydrophilic drugs can be enclosed in the inner watery core [Renukuntla et al., 2013; Kaur et al., 2004]. Liposomes have been effectively used to deliver a variety of components, including proteins, nucleotides etc. [Kurz et al., 2002]. Liposomal encapsulation is one of the preferable methods for the researchers due to their unique encapsulation efficiency towards water-soluble, lipid soluble, and amphiphilic compounds [Sengupta et al., 2021].

iii. Cyclodextrins (CDs): CDs are hollow, truncated cone-shaped cyclical glucose oligomers with an approximate toroidal structure. The fundamental benefit of CDs for use as containers is their structural design. The ability of CDs to form water-soluble complexes with hydrophobic substances is determined by the hydrophobic characteristics of the CD's interior cavity. According to the structural characteristics CDs are classified as follows; α-CD is composed of six glucopyranose residues, β-CD is composed of seven glucopyranose residues, γ-CD is composed of eight glucopyranose residues, and so on.

1.3.3. Metal complexation

Another strategy to increase the bio-efficacy and stability of the PCs is the metal complex formation. A number of metals have beneficial properties that can be bound with PCs, which mitigate their inherent disadvantages. Generally, metal ions can be bound to PCs through the chelation process, which alters the structure of PCs and significantly affects their biological activities and mode of interaction with biological macromolecules [Sengupta et al., 2019]. Specifically, antioxidant activities of PCs are reported to be significantly affected by complexation with metal ions [Sengupta et al., 2019; Xie et al., 2021; Andjelkovic et al., 2006].

1.4. Aim and scope of the work

The primary aim of my thesis work is to explore the interaction of two important phenolic acids, viz. sinapic acid (SA) and gallic acid (GA) (Fig. 1.4), with DNA using various spectroscopic tools. Further, some techniques have been developed to enhance the bioactivity of mentioned compounds. We have selected these compounds due to their potential antioxidant and other bioactivities. SA is a constituent of the hydroxycinnamic acid group, while GA is a member of the hydroxybenzoic acid group.

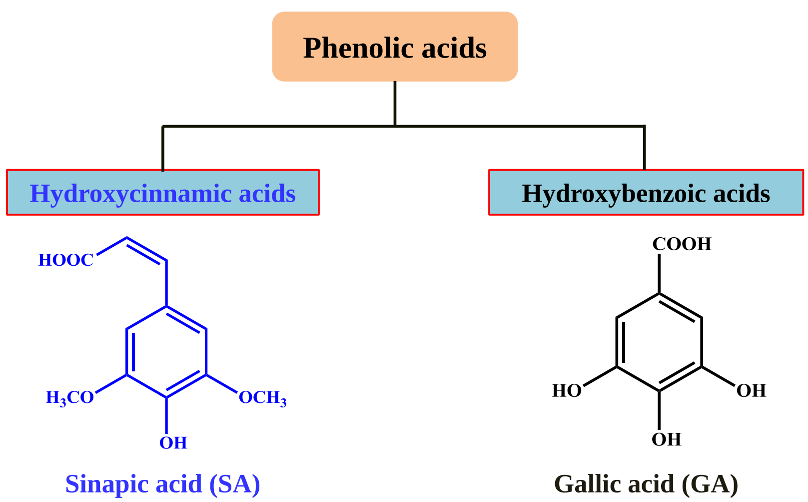


Figure 1.4. Schematic presentation of my molecule of interest for the present work

We have used different approaches to improve the bio-efficacy of phenolic acids and these are discussed in the subsequent chapters. The physicochemical characteristics of the prepared systems and binding interaction were examined using a variety of analytical techniques, including TEM, DLS, zeta potential, FTIR, ITC, NMR, Fluorescence spectroscopy, and UV-Vis spectroscopy. We have also investigated the impact of the changes on the bio-efficacy of phenolic acids by using several in vitro assays such as antioxidant assays, antibacterial assays, release assays, bioaccessibility assays, and cell viability assay. We have also prepared the metal based nanoparticle of phenolic acids and also examined its sensing activity through different analytical tools.

The work presented in the thesis is organized into eight major segments. The organization is as follows:

Chapter 1: This chapter focuses on the structure, functional properties, applications, and difficulties associated with PCs. This chapter also includes a detailed description of PCs interactions with DNA. Finally, the purpose of our work has been briefly discussed.

Chapter 2: This chapter describes the overall idea about the material that we have used during the thesis work as well as the methods that we have used for the work purpose.

Chapter 3A: The interaction of sinapic acid with ct-DNA was described in this chapter. The binding parameters and types of binding between these two were also discussed spectroscopically and this experimental data was also verified by the theoretical study.

Chapter 3B: In this chapter, we discussed a detailed investigation on the in vivo use of sinapic acid to determine its bio-efficacy.

Chapter 4: This chapter elaborately describes the preparation of sinapic acid based Ni nanoparticles and its characterization, sensing application on permanganate ion.

Chapter 5: In this chapter we have discussed the encapsulation of sinapic acid within the micellar core of beta-casein and the effect of encapsulation on some of the bioactivities of sinapic acid. We have also investigated the spectroscopic interactions of sinapic acid with beta-casein.

Chapter 6: The interaction of gallic acid with ct-DNA was investigated through different spectroscopic tools and it was further verified by the theoretical approach.

Chapter 7: This chapter includes a general summary of the overall findings as well as specific conclusions.

Chapter 8: This chapter highlights the limits of the work as well as its potential future possibilities.

1.5. References

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