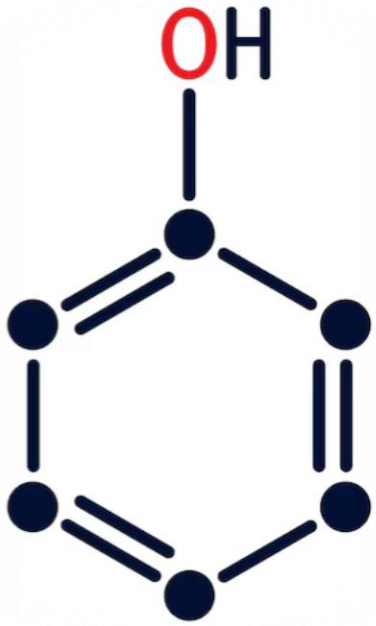
BIOACTIVE COMPOUNDS

Phenols



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mpounds in which an OH group is attached directly to an aromatic ring are designated ArOH (where Ar stands for aromatic) and called phenols. Phenols differ from alcohols in that they are slightly acidic in water. They react with aqueous sodium hydroxide (NaOH) to form salts.

$ArOH_{(aq)} + NaOH_{(aq)} \rightarrow ArONa_{(aq)} + H_2O$

The parent compound, C_6H_5OH, is itself called phenol. (An old name, emphasizing its slight acidity, was *carbolic acid*.) Phenol is a white crystalline compound that has a distinctive ("hospital smell") odour (Figure 23.5a.).

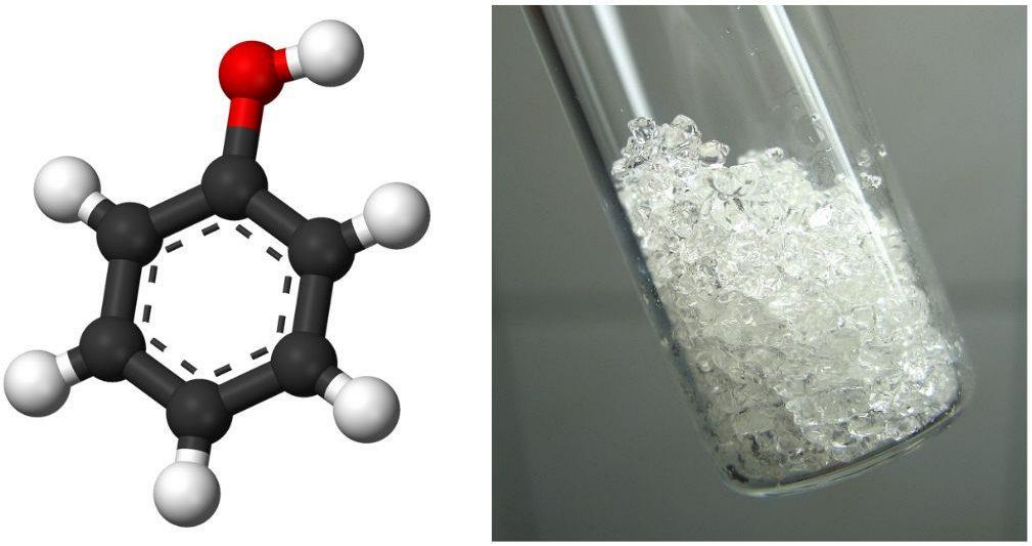


Figure 23.5a. Structure of phenol (left). Crystal form of phenol (right). (credit: *CHEM 1152: Survey of Chemistry II (GSU – Dr. Osborne)*, CC BY-NC-SA 4.0)

Naming Phenols

In the International Union of Pure and Applied Chemistry (IUPAC) system, the rules for naming phenols are similar to naming substituted aromatics.

1. When naming phenols, the parent's name is phenol. This accounts for the benzene ring and the hydroxyl attached to it.
2. The carbon atom bearing the OH group is designated C1, but the 1 is not used in the name.

3. The location of substituents is then determined using the shortest path. The location of all substituents (even if only one is present) must be shown. The name is then determined by indicating the location and identity of the substituents followed by the word phenol.

Example 23.5a

Name the structure in Figure 23.5b.

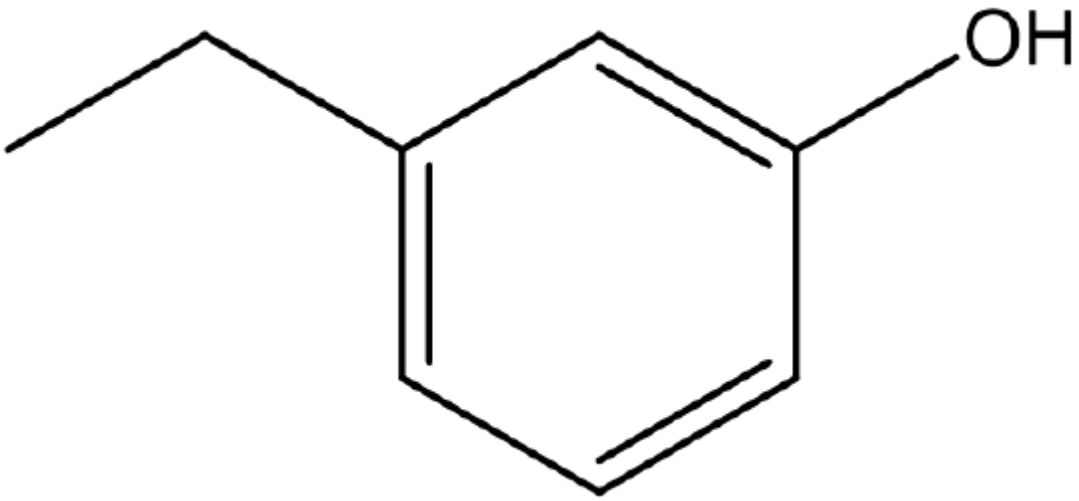


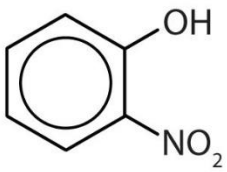
Figure 23.5b. Structure of a substituted phenol (credit: *CHEM 1152: Survey of Chemistry II (GSU – Dr. Osborne)*, CC BY-NC-SA 4.0)

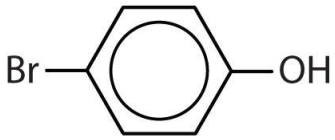
Solution:

According to the naming rules, the name of the molecule is 3-ethylphenol or meta-ethylphenol.

Example 23.5b

Name each compound.

1. 

2. 

Solution:

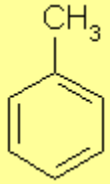
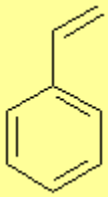
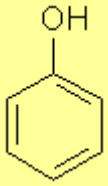
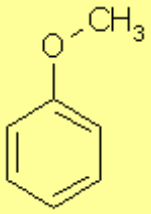
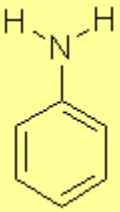
1. The parent chain is phenol and C1 would represent the carbon with the OH attached. There is one substituent present on the adjacent carbon, so the parent chain would be numbered clockwise to represent the shortest path. The substituent, which is identified as a nitro group, is on C2. Therefore, the name of the molecule is 2-nitrophenol (or o-nitrophenol).
2. The parent chain is phenol and C1 would represent the carbon with the OH attached. There is one substituent present on the carbon opposite C1. In this position, the same number is obtained regardless of the chosen path. Therefore, the bromo substituent, is on C4. This indicates that the name of the molecule is 4-bromophenol (or p-bromophenol).

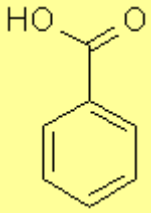
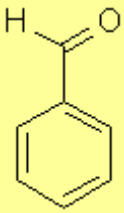
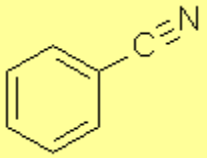
Example source: *CHEM 1152: Survey of Chemistry II (GSU – Dr. Osborne)* ,

Nomenclature:
Functional group suffix = *-common - phenol, systematic - benzenol*
Functional group prefix = *hydroxy*
Numbering of the ring begins at the hydroxyl-substituted carbon and proceeds in the direction of the next substituted carbon that possesses the lower number.

common Substituted Benzenes

- There are many common simple substituted benzenes with common names that are also used as part of the IUPAC system, here are the most important ones that you should know.

Common name	Substituted benzene	Formula
Toluene	Methylbenzene	 $C_6H_5CH_3$
Styrene	Ethenylbenzene	 $C_6H_5CH=CH_2$
Phenol		 C_6H_5OH
Anisole	Methoxybenzene	 $C_6H_5OCH_3$
Aniline	Aminobenzene	 $C_6H_5NH_2$
Benzoic acid		

		 $C_6H_5CO_2H$
Benzaldehyde		 C_6H_5CHO
Benzonitrile	Cyanobenzene	 C_6H_5CN

Ortho, meta or para ? Mono-substituted phenols are characterised using the prefix ortho (*o*-), meta (*m*-) or para (*p*-) depending on the placement of the substituent from the hydroxyl group or the hydroxyl group from a higher priority functional group, 1,2-, 1,3- or 1,4- respectively.

1,2-chlorophenol or *o*-chlorophenol	1,3-chlorophenol or *m*-chlorophenol	1,4-chlorophenol or *p*-chlorophenol

There are several other functional group suffixes, for various substituted phenols, that one needs to know, check here.

Physical Properties:

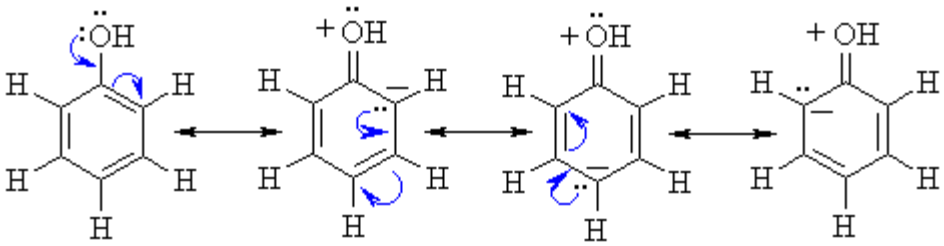
- The polar nature of the **O-H** bond (due to the electronegativity difference of the atoms) results in the formation of hydrogen bonds with other phenol molecules or other H-bonding systems (*e.g.* water). The implications of this are:

- high melting and boiling points compared to analogous arenes
- high solubility in aqueous media

- The presence of *intramolecular* hydrogen bonding is believed responsible for the significantly lower boiling points of certain *ortho*-substituted phenols *vs* the *meta*- and *para*- analogs.

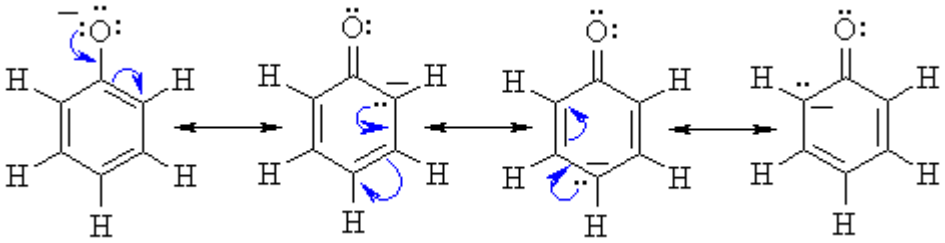
Structure:

- The alcohol functional group consists of an **O** atom bonded to an sp^2-hybridised aromatic **C** atom and a **H** atom via σ bonds.
- Both the **C-O** and the **O-H** bonds are polar due to the high electronegativity of the **O** atom.
- Conjugation exists between an unshared electron pair on the oxygen and the aromatic ring.
- This results in, compared to simple alcohols:
  - a shorter carbon-oxygen bond distance
  - a more basic hydroxyl oxygen
  - a more acidic hydroxyl proton (-OH)



Acidity:

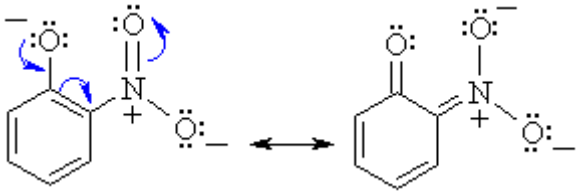
- Phenols are more acidic (pK_a»10) than alcohols (pK_a»16 - 20), but less acidic than carboxylic acids (pK_a»5)
- The negative charge of the phenolate ion is stabilised by resonance due to electron delocalisation onto the ring as shown below:



- The acidity difference means that it is possible to separate phenols from alcohols and/or carboxylic acids.
    - Mixing an ether solution, of either phenol and alcohol or phenol and carboxylic acid, with dilute base (sodium hydroxide and sodium bicarbonate, respectively), results in the stronger acid being converted to its alkali salt, which is then extracted to the aqueous phase and can be separated from the organic phase.
- Nucleophilic substitution reactions of phenols are generally carried out under basic conditions as the **phenolate ion** is a better nucleophile.

Substituent Effects on Acidity

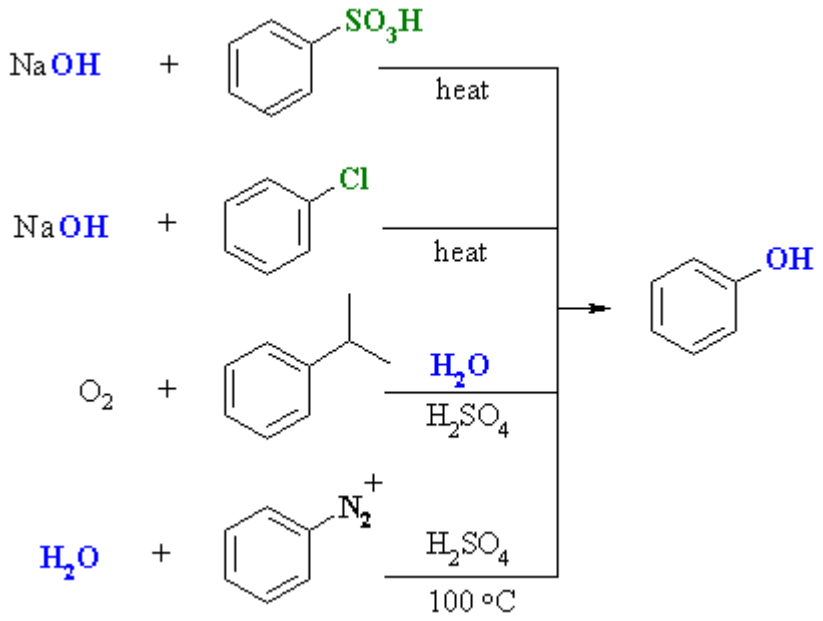
Substituents, particularly those located *ortho* or *para* to the -OH group, can dramatically influence the acidity of the phenol due to resonance and / or inductive effects. Electron withdrawing groups enhance the acidity, electron donating substituents decrease the acidity. The resonance stabilisation of *o*-nitrophenol is shown below:



Compound	pK_a	Compound	pK_a
Phenol	10.0		
o-Methoxyphenol	10.0	p-Methoxyphenol	10.2
o-Methylphenol	10.3	p-Methylphenol	10.3
o-Chlorophenol	8.6	p-Chlorophenol	9.4
o-Nitrophenol	7.2	p-Nitrophenol	7.2
m-Nitrophenol	8.4		

Overview of Phenol Preparations

- Reaction of benzene sulfonic acid with base
- Reaction of chlorobenzene with base
- Acidic oxidation of cumene
- Hydrolysis of diazonium salts



Note: The first three methods are primarily industrial methods while the hydrolysis of diazonium salts is the most important laboratory method.

Phenolic compounds represent a group of molecules and its functions in the growth and development with a defense mechanism in plant. It includes pigments, signaling molecules, and flavors which will protect the plant against insects, fungi, bacteria, and viruses and plays a role to attract or repulse them. This current chapter includes different aspect of phenolic compounds were discussed such as the definition, chemical properties, classification, the biosynthesis process of phenolic compounds, extraction technologies in plants also includes the shikimate, pentose phosphate and phenylpropanoid pathways. They were having many health benefits like UV screens, attractants, signal compounds, and other response chemicals from different types. As per the human physiology, they are vital in protection and plays an important role in prevention and treatment of many chronic diseases. It also acts as antioxidant, antiseptic, anti-proliferative activities, antidiabetic, anti-inflammatory and anti-aging. They are useful to eat such plant foods that contains high antioxidant content, which can hamper the incidence of certain chronic diseases, such as cardiovascular diseases, diabetes and cancers, through the management of oxidative stress. Overall, the phenolic compounds are a gift of god in our day to day lives.

- phenolic compound
- chemical properties
- biosynthesis
- extraction technologies
- health benefit

Grains, mainly cereals and legumes, are important in every diet of human in any part of the world. They are rich in diverse nutrients and phytochemicals, and possess manifold bioactivities, such as antioxidant, antidiabetic, and anticancer effects. Phenolic compounds [PC] are distributed everywhere in most of the plant tissues which includes the parts such as roots, stems, fruits, seeds, leaves, etc.. There are more than 8000 individual plants with great chemicals isolated, structural variability and nearly 200000 were identified with diverse structures and classes from higher plants around the planet. They are classified as primary metabolite and secondary metabolite. The primary metabolite is required for cell nourishment, such as carbohydrates, proteins, fatty acids and nucleic acids. The secondary metabolite is essential to plant survival which directly involved in photosynthetic or respiratory metabolism. As differentiated from primary metabolite, the chemicals and structures of secondary metabolite are responsible for plant defense. They also protect the plant from oxidants and ultraviolet radiation and also act as attracting pollinators or animals for seed dispersion and signal compounds.

The secondary metabolite is classified according to their biosynthetic routes and structure; they are divided into three major groups:

(1) flavonoids, allied phenolic, and polyphenolic compounds.

(2) terpenoids, and

(3) nitrogen-containing alkaloids and sulfur-containing compounds.

These compounds are linked to primary metabolite by biosynthetic enzymes and building blocks Phenolic compounds (flavonoids, allied phenolic, and polyphenolic compounds) are one among the secondary metabolites more cosmopolitan in plants. The shikimate, pentose phosphate and phenylpropanoid pathways are extract from plants. These compounds perform an important role in the growth and reproduction of plants, giving protection against pathogens and predators. In vegetables and fruits, PC contribute to color and sensory characteristics.

The compounds that have one or more hydroxyl groups connected straightway to the ring of an aromatic. The whole category is based on the arrangement of phenol (Figure 1).

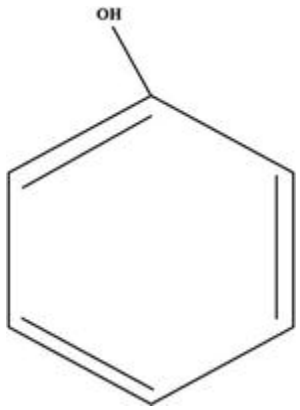


Figure 1.

Phenol.

In phenols, the hydroxyl group is linked to a chain of carbons which are alike to alcohols of aliphatic structures. Due to the existence of the aromatic ring, the phenolic hydroxyl group is affect. The hydrogen of the phenolic hydroxyl is unstable caused by the aromatic ring, that build the phenols as a weak acid

Its structure consists of an aromatic ring that contain 1 or more hydroxyl substituents. It may be classified into simple phenolic molecule and extremely polymerized compounds. The PC occur naturally is associated with one or more phenolic groups when combine with mono- and polysaccharides. In addition, they also can be linked to esters and methyl esters. They have a wide range in structure diversity that occurs in nature. More than 8000 structures of phenolic compound are studied till now

Chemical properties of phenolic compounds

- **Benzene ring**

The carbon's atomic number is 6, i.e. it has 6 electrons and 6 protons. Electrons are around the atom's nucleus in orbitals. The benzene ring is representing one of two mesmeric complex. The double arrow indicates, the two drawn structures and the true structure of the molecule lies in between. Hence, as the six C-C bonds of the ring are identical, with the π-electrons over the entire ring which is more accurate to use structure. The affects of reactivity of aromatic compounds is due to delocalization of the π-electrons is very much favorable and also have tendency to refurbishing aromaticity. Aromatic compounds do not easily undergo any addition reactions and a double bond is replaced by two single bonds, as we see in regular alkenes i.e., linear chains of carbon atoms containing at least one double bond. Aromatic compounds show a partially replaced the reactions, that means the replacement of atoms

Phenolic hydroxyl group

- **Classification**

The word phenolics includes a very wide group of chemical compound. They can be classified in many ways. Harborne and Simmonds (1964) classified these compound into groups depends upon the numeral of carbons in the molecule. (Table 1)

Structure	Class
C6-C1	simple phenolics
C6-C2	phenolic acids and related compounds
C6-C3	acetophenones and phenylacetic acids
C6-C3	cinnamic acids, cinnamyl aldehydes, cinnamyl alcohols
C15	coumarins, isocoumarins, and chromones
C15	chalcones, aurones, dihydrochalcones
C15	Flavans
C15	Flavones
C15	Flavanones
C15	Flavanonols
C15	Anthocyanidine
C15	Anthocyanine
C30	Biflavonyls
C6- C1- C6, C6- C2- C6	benzophenones, xanthones, &$$$;tilbenes
C6, C10, C14	Quinones

Structure	Class
C18	Betacyanine
Lignans, neolignans	Dimers or oligomers
Lignin	Polymers
Tannins	oligomers or polymers
Phlobanhenea	Polymers

Table 1.

Classification of phenolic compounds.

An another classification represented by Swain and Bate-Smith (1962). They categorized the phenols as “common[typical]” and “less common [less typical]”. Ribéreau-Gayon (1972) classified the phenols into three origins which is as follows:

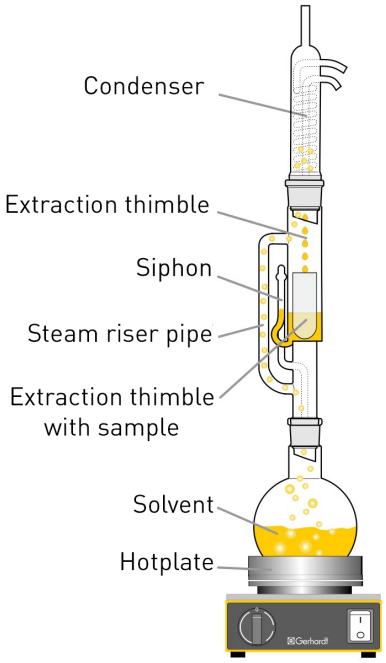
1. It is widely distributed in all plants or in a specific plant.
2. It is less widely distributed to known in confined number of compounds.
3. Phenolic component exists as polymers.

Extraction technologies for phenolic compounds

Solid–liquid extraction

By using aqueous organic solvents from solids, the soluble constituents are removed. The selection of solvents should be accurate so that chemical or physical intervention should be within the matrix. In this method, variable such as temperature, pH, particle size, time, solvent polarity, solid–liquid ratio and riveting should be improved in order to obtained high yields of recovery of the compound which was selected. Few drawbacks of this method includes cost, toxicity, solvent combustible and also prolonged extraction times. It can be used to get PCs from herbal substance. Some methods in this extraction includes the use of poisonous solvents, low cost and can be used in combination with any other extraction techniques.

Soxhlet extraction



It usually contains the matrix with pure and hot solvent. In this way the extracted will be greater in the substance. This method is inexpensive related to energy, time and reactant. Soxhlet extraction were done in small scales in batches and can be adapted to continuously in industrial procedure. The main privilege than novel method, such as ultrasound assisted, microwave-assisted, fastidious fluid, and accelerated solvent extractions in terms of industrial

implementation, consistency, effectiveness, and extract manipulation. The main disadvantage was the sensitivity of some compounds to the temperature conditions of extraction. The variants of this technique are: high-pressure, automated, ultrasound-assisted, and microwave-assisted Soxhlet extraction

- **Pressurized fluid extraction and supercritical fluid extraction**

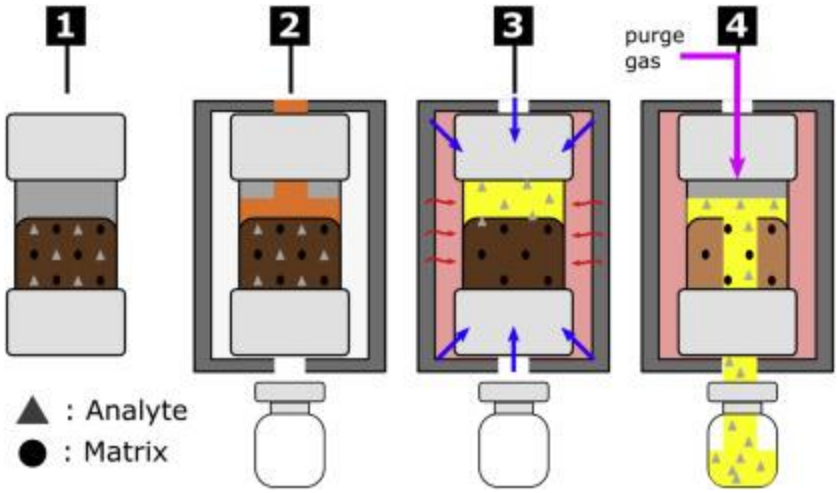


Figure . General principle of ASE.

1) Solid/semisolid sample is placed in sample cartridge.

2) Extraction solvent is added.

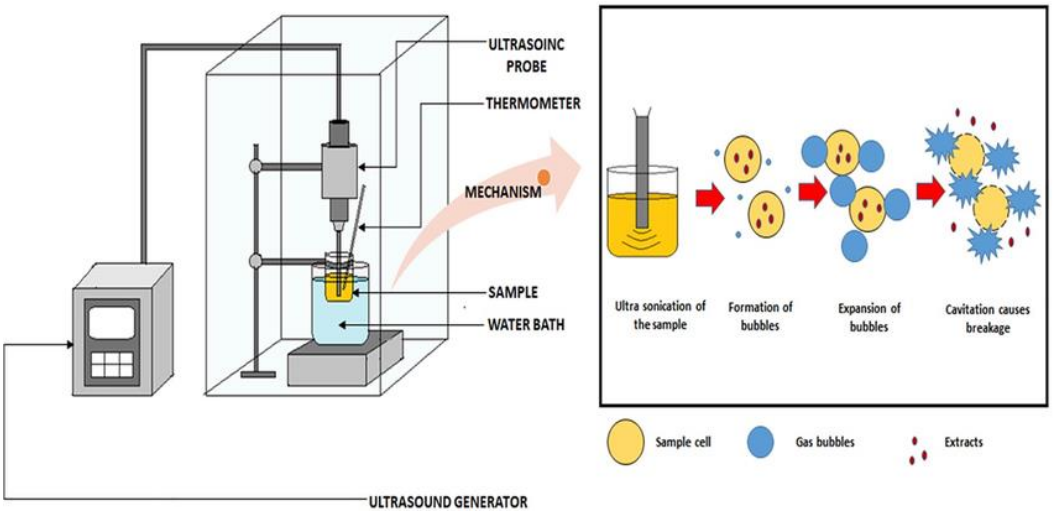
3) Static extraction under elevated temperature and pressure.

4) Purge of the cartridge to extract sample into collection vessel.

The extraction method is like Soxhlet extraction, then again, actually the solvents are utilized in tightening influences close to their supercritical area, so the raised temperature permits a more prominent dispersion and dissolvability of the solute to be extricated. At the point when the high pressing factor applied to the framework, the dissolvable beneath its limit is permitting the better focus in the network. These working conditions permit the utilization of low dissolvable volumes

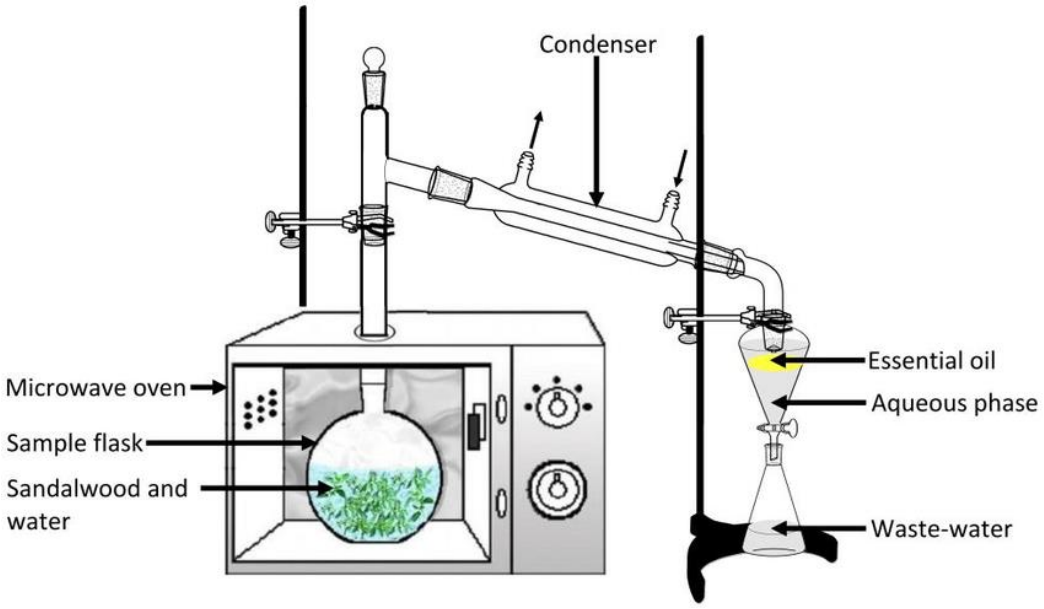
and lessen extraction times. The second extraction strategy comprises of the detachment of a compound (strong or fluid) from a grid, utilizing liquid as a dissolvable under supercritical conditions. Under supercritical conditions a liquid coincides in both fume and fluid states. The most ordinarily utilized liquids is carbon dioxide (CO2), which is joined with ethanol to change its extremity. The upsides of CO2 as extraction liquid are: moderate supercritical conditions (31.1 °C and 73.8 MPa), nonattendance of harmfulness, substance security, simple to reuse, and ease. The upsides of supercritical extraction will be: extraction limit like fluid natural solvents and the concentrates are cleaner. Mechanical utilization of supercritical liquid extraction was restricted since this strategy were created in detachment of other handling steps that are important to acquire an item

- **Ultrasound-assisted extraction**



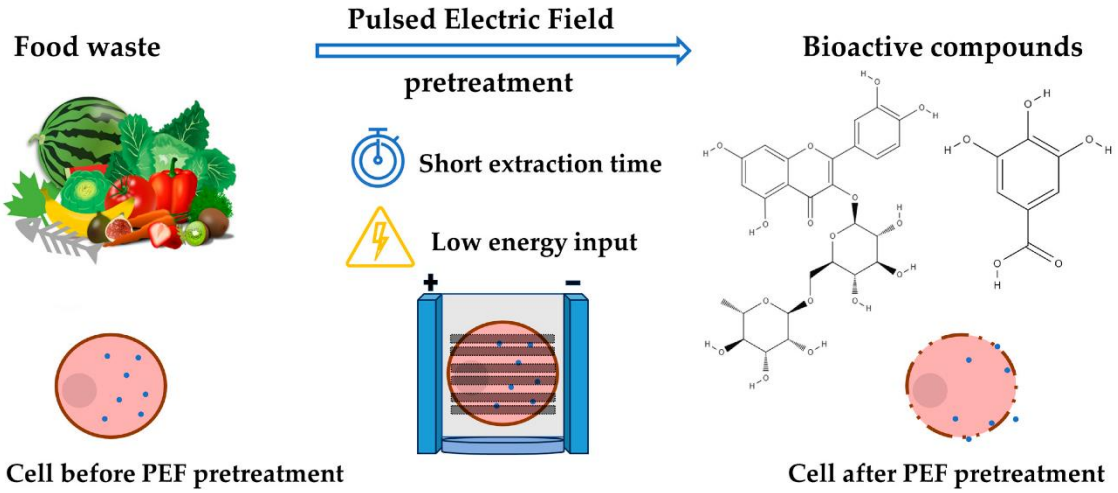
They used to remove bioactive mixtures, similar to cancer prevention agents, fundamental oils, steroids, and lipids from plants. The utilization of ultrasound improves the entrance of the dissolvable into cell materials, encouraging mass exchange and the arrival of the mixtures to be removed. The recurrence of ultrasound impacts the yield and extraction energy. At frequencies >20 kHz sound waves produce extension pressure cycles, in a fluid this outcome in the arrangement of air pockets that develop and breakdown close to the strong network, encouraging extraction

- **Microwave-assisted extraction.**



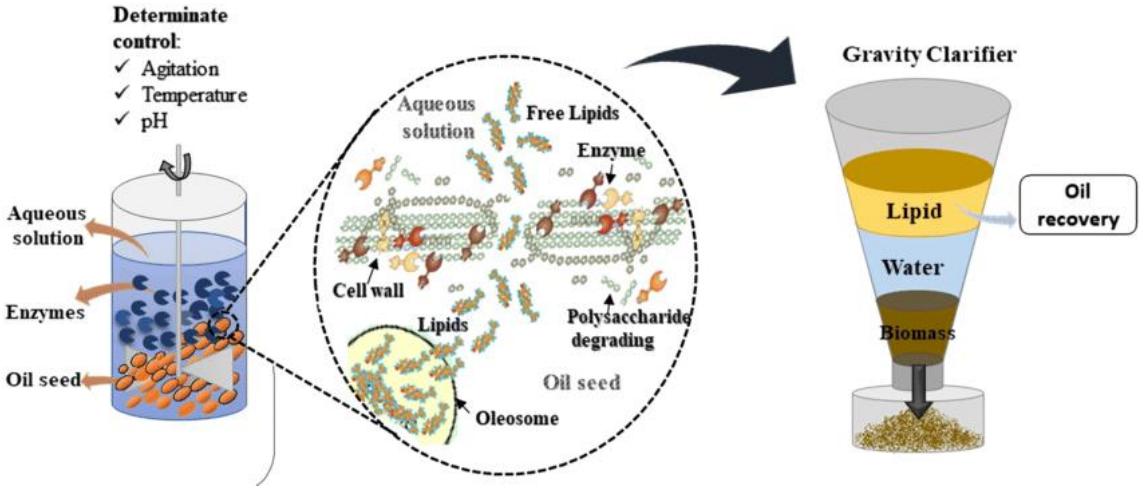
Microwaves are electromagnetic waves comprising of an electric field and an attractive field that waver oppositely to one another at frequencies somewhere in the range of 0.3 and 300GHz. The microwave energy acts straightforwardly on the particles by ionic conduction and dipole revolution, motivation behind why just polar materials can be warmed as such. The microwave-helped extraction relies upon the dielectric defenselessness of both dissolvable and network. Since the water inside the lattice assimilates microwaves, the interruption of the material is controlled by an inward overheating, which likewise improves the recuperation of the extricated compound. Microwave-helped extraction is characterized into shut and open frameworks. In a shut framework, the extractions are done in a fixed vessel under uniform warming; in this framework the high pressing factor and temperature permit fast and proficient extraction. Then again, open frameworks are more reasonable for extricating thermolabile mixtures, since they work under less extraordinary conditions.

- **Pulsed electric field extraction.**



The cellular wall and cell membranes act as protective layer that prevent the bioactive compounds extraction in animal and plant tissues. The transmembrane segment of the cell lead to pores or electroporation by the application of an electric field. The power of the electrical pulses provides is changeable or unchangeable may form the electroporation. The pores are small associated to the whole area of the current or electric and its membrane breakdown may vary. On the contrary, increasing the intensity and time of the treatment, it is irreversible to the permeability of cell membrane

- **Enzyme-assisted extraction**



An alternative method to solvent-based extraction. It depends on the enzymes to selectivity and catalyze reactions in aqueous humor. On the constituent of cell membranes, the enzymes with hydrolytic activity such as cellulases, hemi-cellulases, pectinases, etc. increases cell wall permeability and bioactive compounds extraction was yield such as antioxidants, pigments and compounds with pharmaceutical applications.

- **Medicinal importance of phenolic compounds**

Current studies have associated that consuming the foods are abundant in PC are beneficial in prevention of non-communicable diseases or lifestyle disorder which includes cardiovascular diseases, certain group of cancer, and diseases associated with aging the biological effects acquired from PC were trait to antioxidant properties

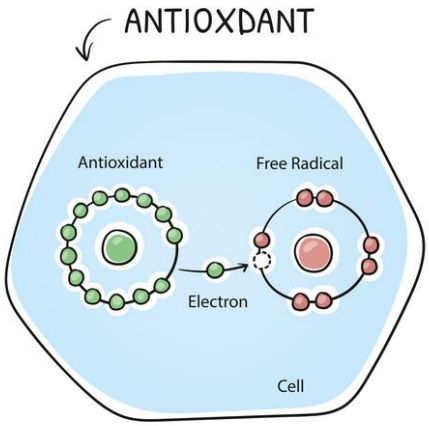
They are as follows.

- **Antiseptic**

PC have effects on human health which was revealed by Bravo in 1998 PC was used phenol as an antiseptic from ancient times. Now a day, it is no longer used due to, its side effects on living tissues that create blister formation specially on high concentrations. As an antiseptic agent, it is effective against the bacterium *Staphylococcus aureus* i.e. 5% (w/v) solution of phenol. It is used as an oral esthetic with the concentration of 1.4% in throat pastille. It is also in sunscreens

lotions. It helps to prevent sunburns due to the presence of the aromatic ring which is an effective absorbance of the UV-B radiation (ranging from 280 and 315 nm) from the sun. It was widely used since the 1970's and nowadays due to the formation of skin rashes and acne the usage is reduced.

Antioxidant

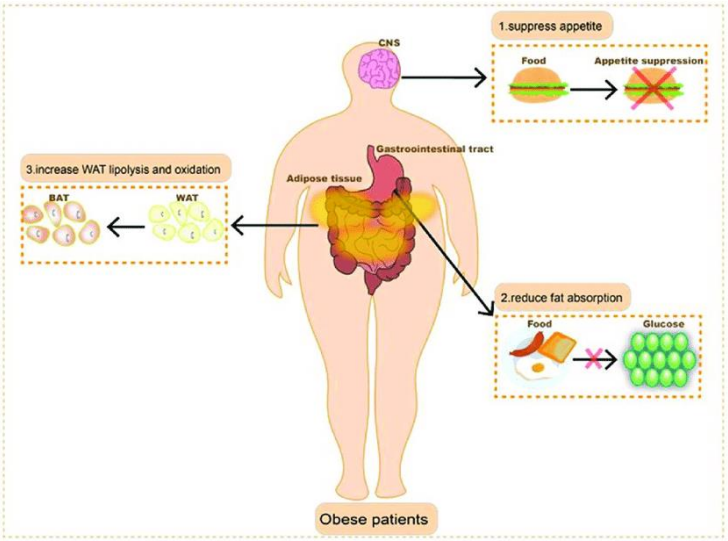


The oxidative damage and an imbalance to large biomolecules, like lipids, DNA, and proteins may be due to overproduction of oxidants in physical body. This damage includes the pathogenesis of many human diseases i.e. cardiovascular diseases (CVD), certain sorts of cancers and aging. Thus, it could be a crucial role for the prevention and treatment of chronic diseases by antioxidant phytochemicals which are demonstrated to have antioxidant abilities in human studies. Compounds are scavenging radicals that are referred as antioxidants. The important anti-oxidants are vitamin C and vitamin E. A lack of vitamin C in the diet leads to scurvy. The symptoms include rotten gums, purple lesions on the skin, loss of teeth etc. Vitamin E is a mixture of α-, β-, γ-, and δtocopherol in that α-tocopherol is the most effective. Vitamin E is lipid-soluble and has the ability to disrupt the chain reaction at the time of lipid peroxidation. They provided many health benefits by antioxidant activity of polyphenols.

Protective against cardiovascular diseases

Polyphenols are helpful for preventing and treating CVD by antioxidant activity and also by other bioactivities such as preventing platelet aggregation. Anti-inflammation and adhesion which includes oxidative stress and other damage because they owe other physiological effects, like blood pressure reduction etc.

Anti-obesity activity

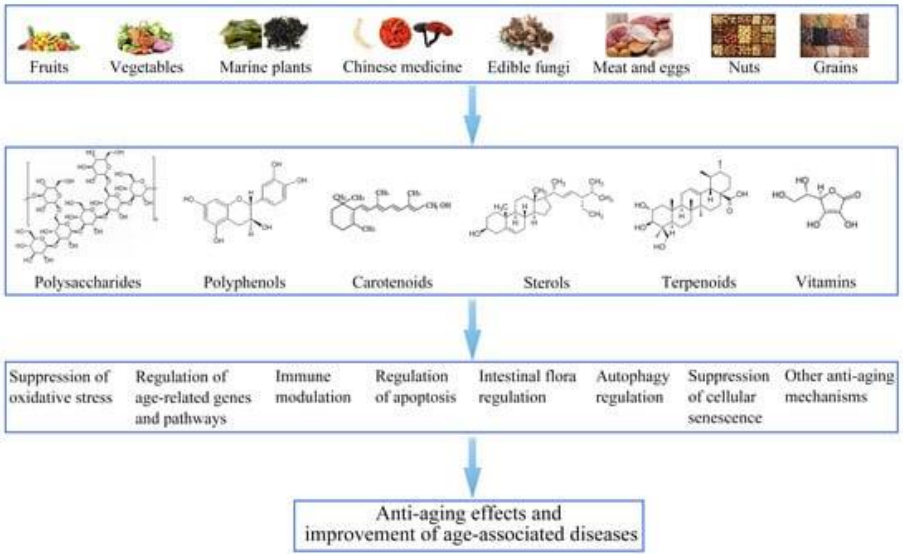


This activity includes quercetin which may be mediated by mitogen-activated protein kinases signaling pathways (MAPK) and the adenosine monophosphate-activated protein kinase (AMPK), respectively in mature adipocytes and pre adipocytes.

Anti-diabetic activity

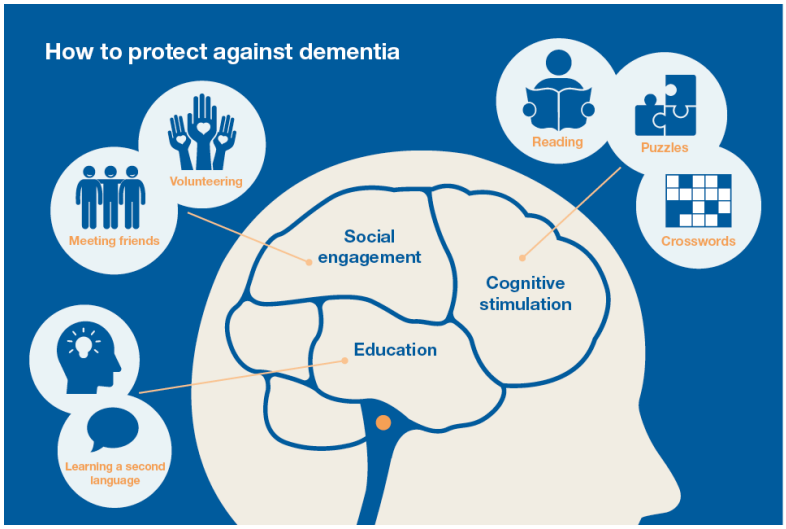
Due to hyperglycaemia and hyperlipidaemia, diabetes is usually associated by expand the yielding of free radicals or oxidative stress. There is a remarkable decrease in plasma antioxidants in diabetes and its complication. The metabolic homeostasis was better, and the development of T2D and its complications was observed in Cohort studies showed that was retard or prevented by taking of whole grain foods. PCs such as flavonoids and phenolic acids are helpful in promoting health by decreasing the high risk of metabolic syndrome and the associated complications of type 2 diabetes

Antiaging activity



An important factor in aging or age-associated degenerative diseases, the free radicals and oxidative stress have been believed as an antioxidant systems are declined during aging. Antiaging activities is explained by different mechanisms and revealed by antioxidant phytochemicals.

Protective action on Alzheimer's disease



It is particularly susceptible due to high concentration of free radicals without appropriate levels of anti-oxidation. In elderly people, the pathogenesis of dementia or AD shows oxidative stress. The study on walnuts shows that polyphenolic compounds help to release the oxidant and decrease the inflammatory signs on the brain cells. It also repairs, the increased neurogenesis, inter-neuronal signaling, upgrade isolation of insoluble toxic protein accumulates, that play a role in preventing AD. Thus, by decreasing the oxidant stress and acetylcholinesterase that may protect or prevent against AD.

Anti- cancer activity

Anticancer activity of natural bioactive.

A huge number of fruits and vegetables in our diet had shown, a decrease risk of human cancers such as breast cancer, lung cancer, colon cancer and prostate cancer. It is revealed that flavonoids are of special attraction and bioactive compounds in plant providing defensing effects. A study shows that in mice, it provides protection against cancer of skin which are caused through ultraviolet radiation or chemical carcinogens by consumption of tea and its polyphenolic constituents.

Miscellaneous

Plant PC provide a means for preventing the side effects that fungal toxins (mycotoxins) and also serving in detoxification. Many of the volatile PCs, such as the main PC of cloves i.e. eugenol (a hydroxyphenyl propene), or a typical component of oregano i.e. carvacrol (phenolic terpene), curcuminoids or Curcumin (diferuloylmethane) are which found only in the rhizomes of *Curcuma longa* [turmeric] are achieved. Curcumin as we all known plays an important role of various illnesses from cancer to autoimmune, neurological, cardiovascular, and diabetic etc. in the form of preventing and treating diseases.

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