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Computer Aided Drug Design of Novel Active Polyphenols: QSAR Approach

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"On no soul doth Allah Place a burden greater than it can bear..." [2:286]

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Abbreviations

ABTS 2,2'-Azino-Bis 3-Ethylbenzthiazoline-6-Sulphonic acid

BDE Bond Dissociation Enthalpy

CAA Cellular Antioxidant Activity

CUPRAC Cupric Ion Reducing Antioxidant Capacity

DFT Density Functional Theory

DPPH 1,1-Diphenyl-2-PicrylHydrazyl

ELC Enhanced Chemiluminescence

EPS Electrostatic Potential Surfaces

ETE Electron Transfer Enthalpy

FRAP Ferric-Reducing Antioxidant Power

HAT Hydrogen-Atom Transfer

HF Hartree – Fock

HOMO Highest Occupied Molecule Orbital

IP Ionization Potential

IUPAC International Union of Pure and Applied Chemistry

KS Kohn – Sham

LDA Local density approximation

LDL Low-Density Lipoproteins

LSD Local-Spin-Density

LUMO Lowest Unoccupied Molecular Orbital

MEPS Molecular Electrostatic Potential Surface

MM Molecular Mechanics

MD Molecular Docking

MMFF94 Merck Molecular Force Field

MMFF94s Merck Molecular Force Field Static

MOPAC Molecular Orbital PACkage

NSAIDS Non-Steroidal Anti-Inflammatory Drugs

ORAC Oxygen Radical Absorbing Capacity

PA Proton Affinity

PC	Phenolic Compounds
PDE	Proton Dissociation Enthalpy
QSAR	Quantitative Structure-Activity Relationship
RNS	Reactive Nitrogen Species
ROS	Reactive Oxygen Species
SAR	Structure-Activity Relationship
SE	Semi-Empirical
SET-PT	Single Electron Transfer followed by Proton Transfer
SPLET	Sequential Proton Loss Electron Transfer
TEAC	Trolox Equivalent Antioxidant Capacity
TRAP	Total Radical Trapping Antioxidant Parameter
UFF	Universal Force Field

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Theoretical Framework

Introduction

Polyphenols are micronutrients; they are phytochemical compounds that include flavonoids, tannins, stilbenes, coumarins, and phenolic acids [1]. These compounds are widely found in human food such as fruits, vegetables, nuts, etc [2] The evidence for their preventive role from degenerative diseases has emerged and their positive effects on human health depend on their bioavailability, the consumed amount, and most importantly on their antioxidant property. Polyphenols have been subject to studies for their antioxidant property (also known as antiradical property), which refers to their ability to prevent harmful damages caused by Reactive Oxygen Species (ROS) [3]. This preventive property -known as the radical scavenging- is processed by various chemical mechanisms such as Hydrogen Atom Transfer (HAT), Single Electron Transfer followed by Proton Transfer (SET-PT), and Sequential Proton Loss Electron Transfer (SPLET). Furthermore, these phytochemicals have a large specter of biological properties including anti-cancer [4], anti-bacterial [5], anti-microbial [6], anti-viral [7], etc.

In order to design and synthesize new potent polyphenols, different strategies were investigated. The QSAR (Quantitative Structure-Activity Relationship) approach is one of them. In this work, the QSAR approach will be adopted to model the polyphenol biological activity in function of selected molecular descriptors such as: structural, semi-empirical, Density Functional Theory (DFT) based descriptors, etc. The main purpose of this investigation is to (1) generate robust QSAR models, and (2) use them -combined with specific algorithms- to propose (for experimentalists) new potent polyphenols agents.

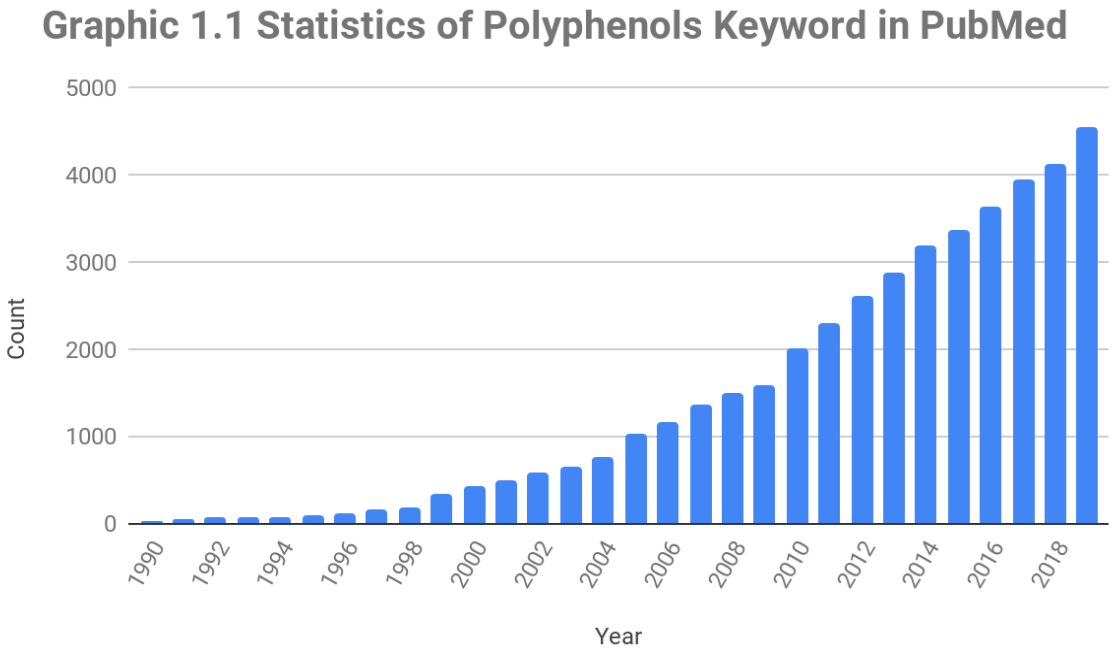
I. Chapter Chemistry of the Phenolic Compounds

1. History

Literature sources seem to agree that the Ancient Greeks of the archaic period (ca. 800–500 BC) were the first in Europe to develop the technology of plant extraction containing them in the conversion of animal skins into leather with the use of oak galls. The first mention of polyphenols; known then as "vegetable tannins", was in the classical literature accredited to Theophrastus of Eressus (371–286 BC). Until the beginning of the 20th century, one of the main sources of natural tanning materials was the quebracho heartwood, produced at the time almost exclusively on a large scale in South America, especially Argentina and Paraguay. Later the leather industry in Germany could become independent from the tanning importation after the development of an industrial process extracting tanning materials from oak trees abundant in the south of the country. [8]

Phenol was isolated from coal tar in 1834 by Runge. Fast-forwarding to 1841 where the first pure polyphenol was prepared by Auguste Laurent. Until World War II, phenol was essentially a natural coal-tar product. Eventually, synthetic methods replaced extraction from natural sources. [9]

As has been mentioned, the existence of polyphenols has been known for many years. However, the interest in them has increased sharply in the past two decades especially among food scientists, nutritionists, the agricultural industry, and consumers. [10] This rise is essentially due to their biological properties and it is evidenced by the relative amount of research publications [11]. We found that 22 articles had been published in 1981, 33 in 1990, 93 in 1995, 175 in 1998, and 592 in 2002. Furthermore, according to more recent PubMed statistics, the number of articles that have been published in 2005 is 1031 whereas for 2010 it is 2010, 3364 in 2015, and 4542 in 2019 and as for 2020 up to now there are currently 1564. **Graphic1.1** below demonstrates the impact of polyphenols in research literature during the past 30 years.



2. Phenols and Polyphenols

In phytochemistry, phenolic compounds are considered as model systems as well as being studied on a large scale. [12] Phenolic compounds represent the majority of secondary plant metabolites. [13] Polyphenols are a large group of molecules with a variety of functions playing an important role in plant growth, protecting tissues, development and defense strategies especially against insects, fungi, bacteria, and viruses. [14] [15] Along with giving color and flavor to plants. [12]

Polyphenols are found in the daily human dietary [16] where approximately a mean intake is 1 g per day. [17] Polyphenols can be found in a variety of beverages and food such as whole grains, vegetables, fruits, wine, and tea. These compounds are basically non-toxic and efficient phytochemicals. Polyphenols are antioxidants capable of preventing degenerative diseases such as

hyperlipidemia, hyperglycemia, hypercholesterolemia, and cancer etc. Polyphenols are the most popular antioxidants in the human diet. [16]

On account of the diversity of polyphenols, these latter are usually classified by various criteria, such as their chemical structure, biological function, and source of origin. [17] [18]

Phenolic compounds represent a broad category of semi-water-soluble compounds. [19] Their aromatic ring is directly linked to one or several hydroxyl groups. As seen in **Figure 1.1**

Phenol is the structure upon which the entire group is based. The aromatic ring in this case is benzene.

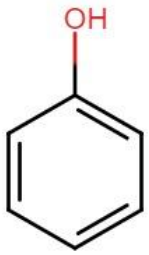
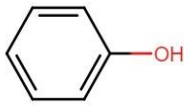


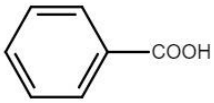
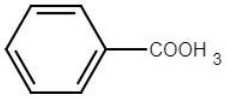
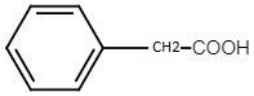
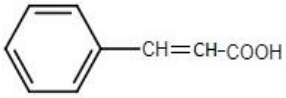
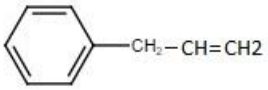
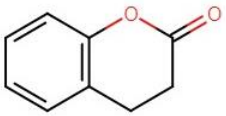
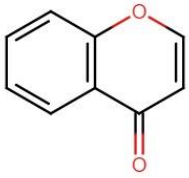
Figure 1.1 Phenol Structure.

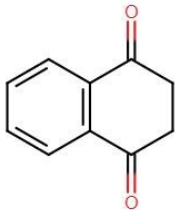
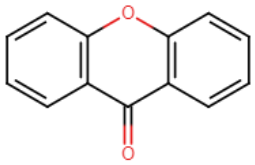
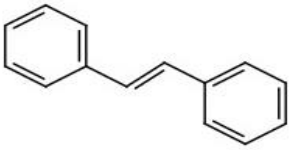
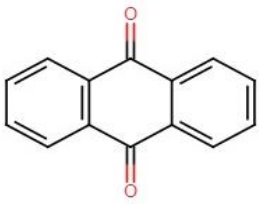
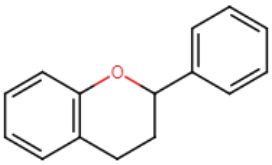
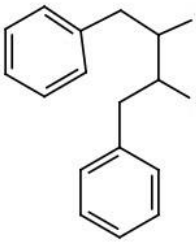
The phenols are in many ways similar to alcohols of aliphatic structures where the hydroxyl group is attached to a chain of carbons. However, the phenolic hydroxyl group is influenced by the presence of the aromatic ring. Because of the aromatic ring, the hydrogen of the phenolic hydroxyl is labile, which makes phenols weak acids. [15] Polyphenols are capable of reducing reactive oxygen species and various organic substrates and minerals. These redox properties explain the considerable interest in their role in the prevention of several major chronic diseases associated with oxidative stress, such as cardiovascular diseases, cancers, type II diabetes, neurodegenerative diseases or osteoporosis. [17] As already mentioned phenolic has a variety of structures (over 800) these structures extend from single substituted phenolic ring to highly polymerized substances.

This group of natural products is highly diverse and contains several sub-groups of phenolic compounds. [18] The main sub-groups would be phenolic acids, flavonoids, stiblins, phenolic alcohols, and lignans **Table 1.1**. [16]

Table 1.1 Main Classes of Phenolic Compounds. [20]

Class	Basic Skeleton	Basic Structure
Simple phenols	C_6	

Benzoquinones	C_6	
Phenolic acids	C_6-C_1	
Acetophenones	C_6-C_2	
Phenylacetic acids	C_6-C_2	
Hydroxycinnamic acids	C_6-C_3	
Phenylpropenes	C_6-C_3	
Coumarins, isocoumarins	C_6-C_3	
Chromones	C_6-C_3	

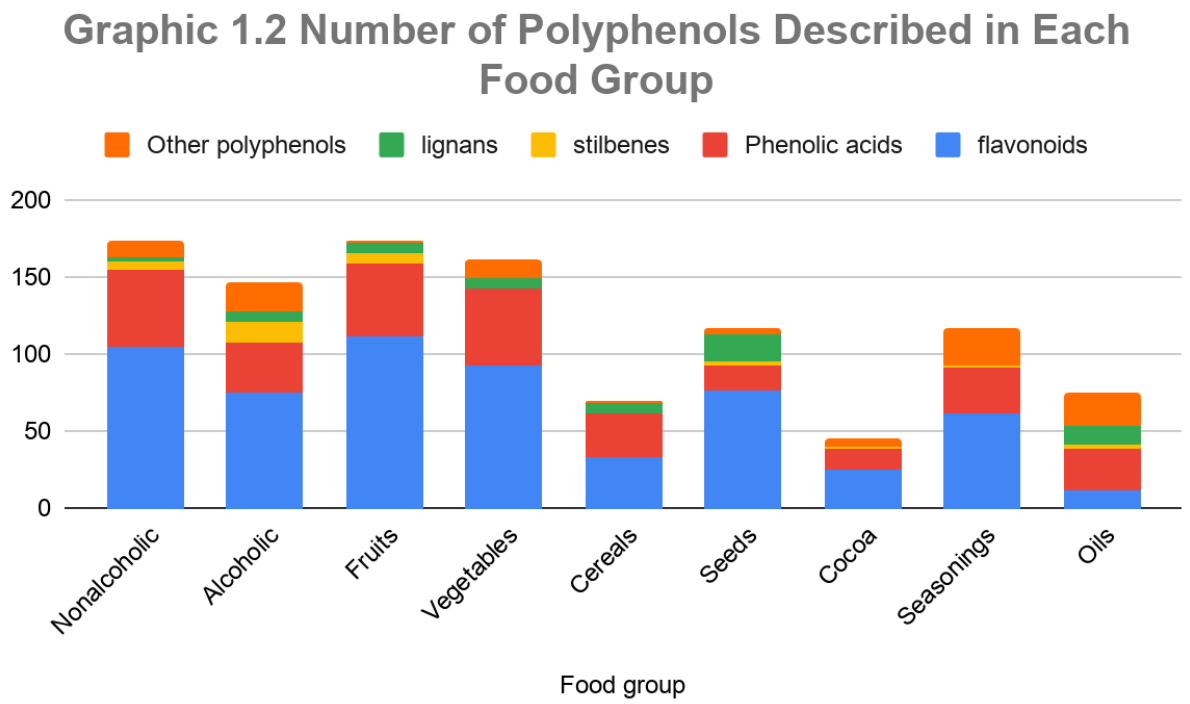
Naftoquinones	C_6-C_4	
Xanthones	C_6-C_1-C_6	
Stilbenes	C_6-C_2-C_6	
Anthraquinones	C_6-C_2-C_6	
Flavonoids	C_6-C_3-C_6	
Lignans, neolignans	$(C_6$-$C_3)_2$	
Lignins	$(C_6$-$C_3)_n$	

3. Polyphenols Bioavailability

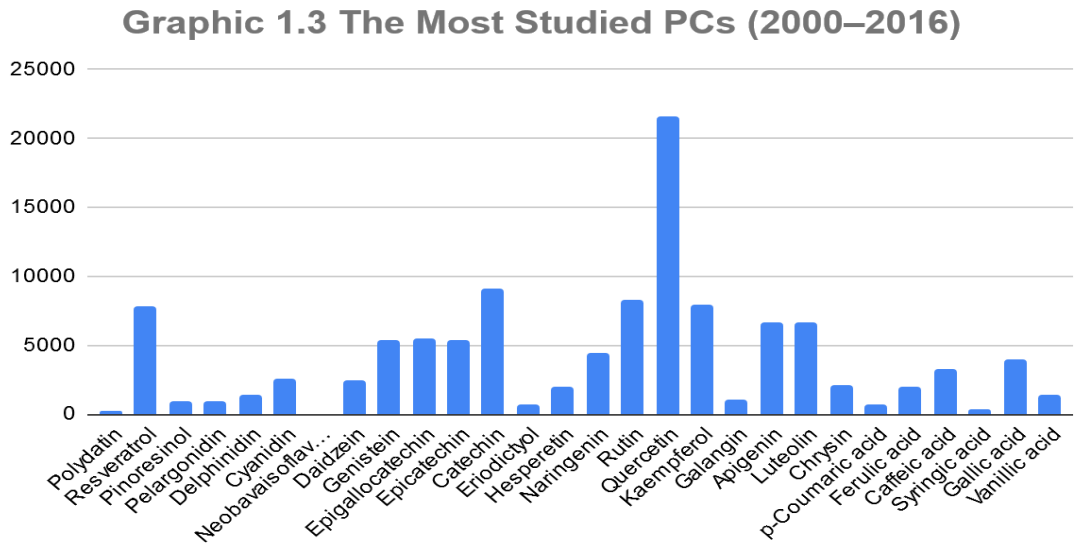
Several thousand polyphenols have been characterized in plants and several hundreds of them are found in food plants. Dietary polyphenols differ widely in their physicochemical properties, bioavailability, biological properties, and health effects. About 1 g of polyphenols per day is commonly ingested with foods, which is significant when compared with the estimated daily consumption of other phytonutrients, such as carotenoids, vitamin E, and vitamin C estimated at 5, 12, and 90 mg per day, respectively. Therefore, polyphenols are the most abundant antioxidant in the diet, i.e., about 10 times higher than the intake of vitamin C and 100 times that of vitamin E. [9] [10] Polyphenol and antioxidant content in the 100 richest foods are summarized in the Annex. [17]

Fruits such as cherry, berries, apples, grapes, pomegranate juice, pears, apricots represent the main sources of polyphenols. For instance, berries contain up to 200-300 mg of polyphenols per 100 g fresh weight. In addition, vegetables, such as carrot, tomato, garlic, cabbage, and celery. and beverages such as wine (white and red), coffee, and tea (green and black). Typically, a glass of red wine or a cup of tea or coffee contains about 100 mg polyphenols. Cereals, nuts, seeds, flowers, bark, propolis, olives, oil, chocolates and other cacao products, and dry legumes like kale, onions, and broccoli also contribute to the polyphenol intake. The bioavailability and the respective intake of polyphenols can differ greatly but most importantly it can determine the health effects of polyphenols. [9] [10] [13] [14] [16]

Over 150 polyphenols are found in each of the three following food groups: nonalcoholic beverages, fruits, and vegetables. Between 45 (cocoa products) and 147 (alcoholic beverages) compounds have been described in any of the other food groups. **Graphic 1.2** the relative table to the histogram is found in Annex. Herbs and spices found in the seasoning group often contain very high concentrations of phenolic compounds.



As depicted in **Graphic 1.3** (the relative table to the chart is found in Annex), Quercetin, Catechin, Kaempferol, Resveratrol, Apigenin, and Luteolin may be the most-studied Polyphenols in the scientific literature. Flavonoids are a primary class of phenolic compounds that are found in nature. Hence, why a greater focus has been paid to them. Namely, Quercetin is the most researched of flavonoids, these research have proven the pharmacokinetic profile of this compound.



4. Benefits of Polyphenols

Interest in polyphenols has typically been linked to their organoleptic properties, such as taste, color, bitterness (flavonols), and astringency (tannins). [10] It is no secret that phenolic compounds play an important role in the color, bitterness and astringency of red wine and contribute to its sensory profile and a number of other tactile or mouth feel characteristics. [14]

These phytochemicals are known to have a variety of critical roles in the adaptation of plants to their environment [13] and in plant physiology. Polyphenols play an essential role in defense against plant pathogens as well as animal herbivore attacks, they also respond to various abiotic stress conditions, such as rainfall and ultraviolet radiation. [6] Also as a signaling compound in reproduction, pathogenesis, and symbiosis (involved in response mechanisms against stress). [10] Additionally, polyphenols provide flower, fruit, and seed pigmentation, thus attracting pollinators and seed dispersers; promote plant fertility and germination of pollen; act as signal molecules in plant-microbe interactions, protect against ultraviolet light, and have other defensive functions. [21]

In recent times the nutritional value of polyphenols has been getting more acknowledgment, [10] as well as for their ability of regulation of metabolism, weight, chronic disease, cell proliferation, and generally for their role in human health [22]. They can act as anti-allergic agents, antimicrobial, anti-inflammatory, antioxidants, anticancer, and antihypertensive. [6]

Phenolic compounds are perhaps the largest and most studied group of phytochemicals that have potential involvement in the prevention of diseases, such as cardiovascular disease, cancer, osteoporosis, diabetes mellitus, liver disorders, obesity, neurodegenerative diseases (Parkinson/Alzheimer's) and skin injuries [6] [12] [13] [23]. In general, they have a positive effect on health that has been attributed initially to their antioxidant, free radical scavenger, and metal chelator properties, then to the capability of inhibiting or reducing different enzymes, such as lipoxygenase, telomerase, cyclooxygenases, and in more recent years, to the interaction with signal transduction pathways and cell receptors, [6] which increases antioxidant activity and prevents cellular oxidation. [10] Maintaining bioactivity, stability, and bioavailability of the active ingredients is what settles polyphenols effectiveness. [24]

As previously stated, many interesting results indicate strong positive correlations between the dietary intake of polyphenol-containing food and the prevention of major diseases [12], thus

they represent an important source of active pharmaceuticals. [13] The role of fruits and vegetables in disease prevention is partly due to their antioxidant properties (polyphenols: vitamins E and C, and the carotenoids). Researches have shown that many polyphenolic compounds are more effective antioxidants in vitro than vitamins E or C, which explains the protective effects in vivo. [14]

5. Polyphenols Classes

The two classes of polyphenols are flavonoids and non-flavonoids. Non flavonoids include structurally simple molecules, such as phenolic acids (hydroxybenzoic acids and hydroxycinnamic acids) and stilbenes (resveratrol, pterostilbene, piceatannol), and lignans (pinoresinol, podophyllotoxin, steganacin) and tannins. On the other hand, flavonoids are the most studied class of polyphenols, includes more than 9,000 identified compounds [25] [10] Figure **1.2**. Polyphenols can be classified by their chemical structure, source of origin, and biological function. In terms of their chemical structure, phenolic compounds have at least one aromatic ring with one or more hydroxyl groups. [26]

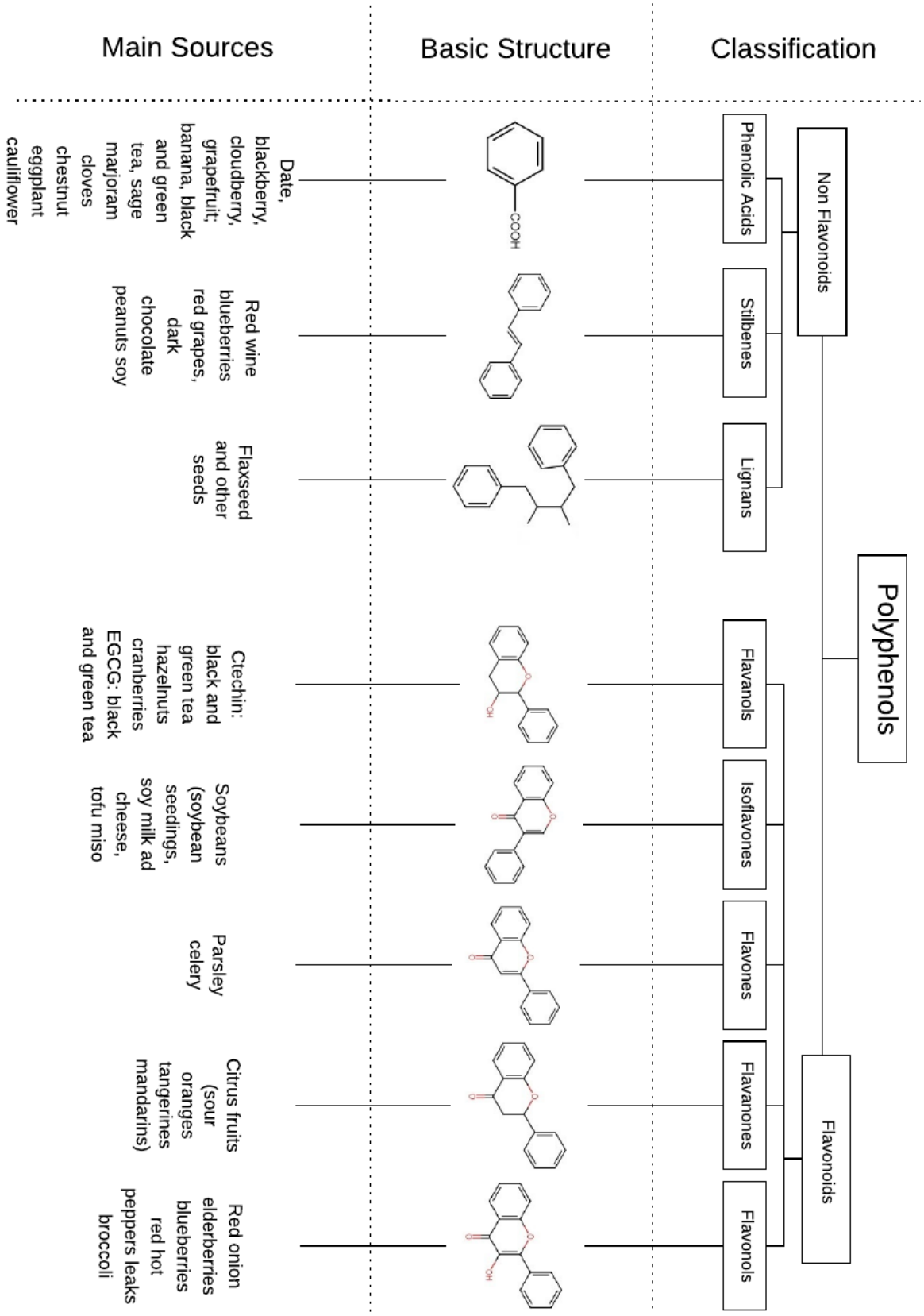


Figure 1.2 Polyphenols Classes

5.1 Flavonoids

The discovery of flavonoids was in the 1930s, and owing to their effect on capillary permeability they were originally introduced as “vitamin P”. [27] (Flavus means yellow in Latin, the name flavonoids for this group was applied by Geissman in 1949) [10], many of these compounds are yellow in color, as the Latin name root suggests [10] [28]. Within the plant kingdom flavonoids are omnipresent; they are the most common pigments next to carotenoids and chlorophyll. [29] Flavonoids are low molecular weight polyphenolic phytochemicals, derived from the secondary metabolism of plants which together with other plant phenols share a common origin: the amino acid phenylalanine and the acetate coenzyme A ester. Flavonoids play an essential role in various biological processes. They also exhibit various types of beneficial properties for human health. [10] [28]

Flavonoids are the largest polyphenols found in our dietary [30], depending on the diet. It is estimated that the daily human intake of flavonoid can range from 50 mg to 800 mg. [31] Flavonoids are found in a vast variety of edible plants, fruit, vegetables, and beverages such as tea, coffee, beer, and wine. [28] However, flavonoids are mainly found in the epidermis of leaves and the skin of fruits [10] Another significant source of flavonoids is different medicinal plants and related phytomedicines. [29]

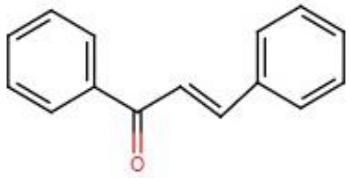
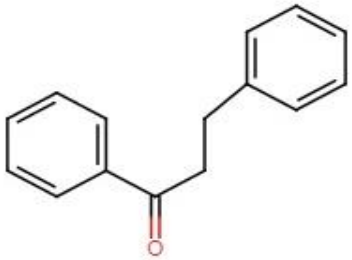
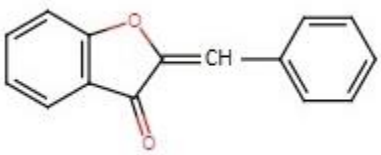
A diet rich in flavonoids has been reported to have beneficial effects on human health; their actions are potentially beneficial in a wide range of diseases, from cardiovascular disease to reduce the risk of certain cancers and neurodegenerative conditions where they protect the central nervous system. Furthermore, many studies have shown the antioxidant power of particular flavonoids and flavonoid-rich extracts and their ability to augment oxidative defense, promote vascular health, and protect the central nervous system. [30] [31] Flavonoids have a variety of important physiological roles in the ecology of plants, they provide plant colors present in flowers, fruits, and leaves and taste of many fruits and vegetables. [10] Also due to their attractive colors, flavones, flavonols, and anthocyanidins may act as visual signals for pollinating insects. Finally, because of their UV-absorbing properties, flavonoids protect plants from the UV radiation of the sun and scavenge UV-generated reactive oxygen species. [29]

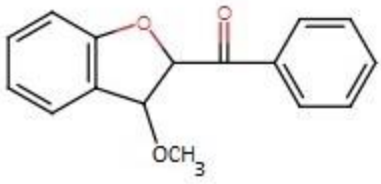
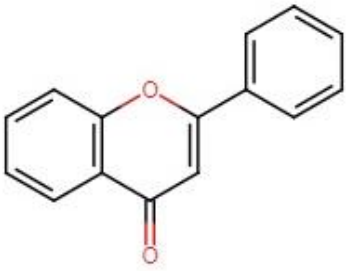
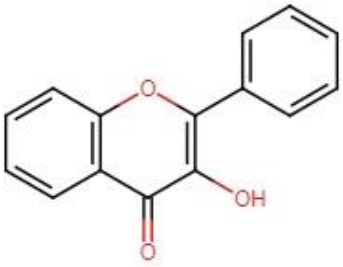
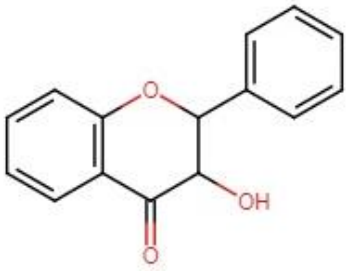
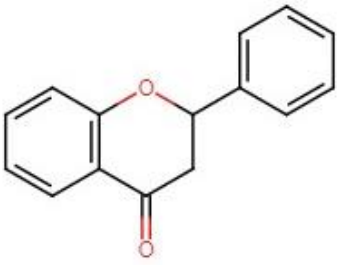
“Flavonoids can be classified into various classes i.e. Flavonols (Quercetin, Kaempferol, Myricetin, Fisetin), Flavones (Luteolin, Apigenin), Flavanones (Hesperetin, Naringenin), Flavonoid Glycosides (Astragalin, Rutin), Flavonolignans (silibinin), Flavans (Catechin,

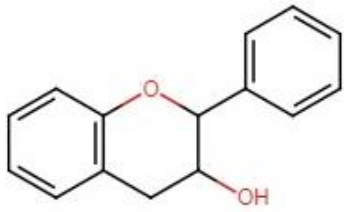
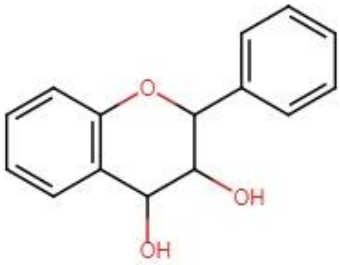
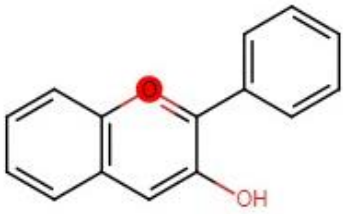
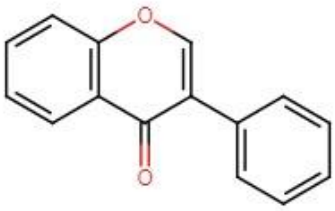
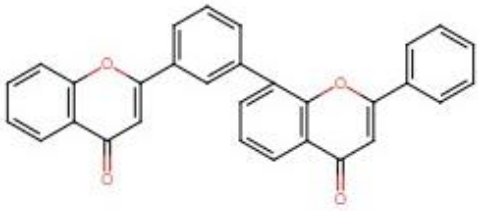
Epicatechin), Isoflavones (Genistein, Daidzein), Anthocyanidins (Cyanidin, Delphinidin), Aurones (Leptosidin, Aureusidin), Leucoanthocyanidins (Teracacidin), Neoflavonoids (Coutareagenin, Dalbergin), Chalcones. All classes of flavonoids exhibit variety of biological activities" [28]

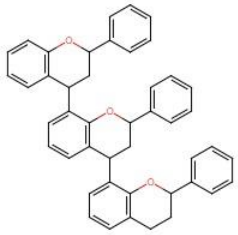
The structural differences in each flavonoid subclass result from variations in the number/substitution pattern of the hydroxyl and methoxy groups, as well as different glycosylation patterns, and the presence of a C2-C3 double bond in the heterocycle pyran ring. These structural variations are responsible for differences in antioxidant activities of flavonoids compounds. [10] Flavonoids are built of two benzene rings that may be connected with three carbon chains from the nearby pyran ring. The general backbone structure of flavonoids is C6-C3-C6, and it contains two units of phenolic nature(C6). Most flavonoids have a structure in which C2 of C ring is attached with B ring, but C3 and C4 attachments are also found. **Table 1.6** [18]

Table 1.6 Classification of Flavonoids. [20]

Flavonoid	Basic Structure
Chalcones	
Dihydrochalcones	
Aurones	

	
Flavones	
Flavonols	
Dihydroflavonol	
Flavanones	

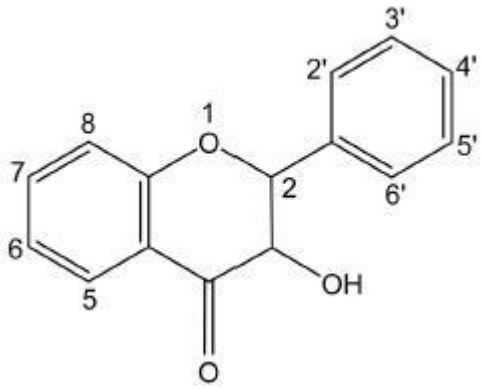
Flavanol	
Flavandiol or leucoanthocyanidin	
Anthocyanidin	
Isoflavonoids	
Biflavonoids	

Proanthocyanidins or condensed tannins	

5.1.1 Flavonols

Flavonols are the most ubiquitous and the most widely distributed flavonoid compound in nature as well as the most active compound. They derive from 3-hydroxyflavone, the simplest flavonol. The most frequent flavonol and the most abundant in plants is Quercetin, which is a potent antioxidant because it has all the right structural features for free radical scavenging activity in results it's also the best studied. . [14] [27] [32] [33] **Table 1.7**

Table 1.7 Flavonols Basic Structure and Examples [29]



Position compound	5	7	3'	4'	5'
Quercetin	OH	OH	OH	OH	-
Kaempferol	OH	OH	-	OH	-
Galangin	OH	OH	-	-	-
Fisetin	-	OH	OH	OH	-
Myricetin	OH	OH	OH	OH	OH

Flavonols are usually present in glycosylated forms in large amounts in our normal diet. Frequently associated with a sugar moiety often glucose or rhamnose, Flavonols, are widely distributed in plants and are present in considerable amounts in fruits and vegetables. Flavonols are generally present at relatively low concentrations of (15–30 mg/kg fresh weight). The richest sources include onions (up to 1.2 g/kg fresh weight), curly kale, leeks, broccoli, apples, cider, grapes, and blueberries. Red wine and tea also contain up to 45 mg/L flavonols **Table 1.8**, (the full length table is in Annex). [14] [27] [32]

Table1.8 Flavonols Content in Foods

Flavonols	Source	Content by wt or vol mg kg^{-1} fresh wt (or mg L^{-1})
Quercetin	Curly kale	300–600
Kaempferol	Leek	30–225
Myricetin	Cherry tomato	15–200

Flavonols formation usually depends on light so that they are mainly concentrated in the external tissues. The concentration of flavonols in free standing leaves exceeds that in other parts of the same plant and even on the same piece of fruit, except in onions. This is due to the light exposure to their different edges. [16] [34]

Flavonols have a considerable extent of biological activities. The beneficial effects of diets rich in fruits and vegetables on cardiovascular health have been often credited to flavonoids in general and more specifically to flavonols. Flavonols are commercialized as dietary supplements either as pure compounds (e.g. quercetin), flavonoids mixtures or extracts, often at doses that exceed by far the dietary intake. Some flavonoids are also used as venotonic drugs for the treatment of several venous diseases. [32] Moreover Flavonols act as antioxidants and protect the ascorbic acid from auto-oxidation, for example in fruit juices. Also flavonols can lead to discolourations.[34] In addition to their antioxidant effect and the biological activities in common with flavonoids, flavonols interfere with a large number of biochemical signaling pathways. Therefore, physiological and pathological processes. There is solid evidence that, in vitro, quercetin and related flavonols exert endothelium-independent vasodilator effects, protective effect on nitric oxide and endothelial function under conditions of oxidative stress, platelet

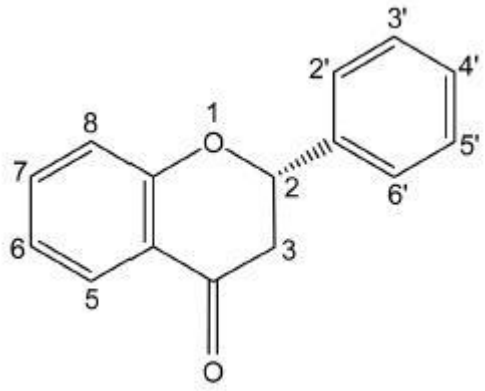
antiaggregant effects, inhibition of LDL oxidation, reduction of adhesion molecules and other inflammatory markers and prevention of neuronal oxidative and inflammatory damage. [32]

5.1.2 Flavanones

A few decades ago, flavanones were considered as only minor flavonoids, like chalcones, dihydrochalcones, dihydroflavonols, and aurones. However, during the past years, the total number of known flavanones has increased [25] and they captured much interest to the researchers working with flavonoids and the related molecules in chemistry and the biological sciences [35]. Which made them emerge as one of the most interesting subclasses of naturally occurring flavonoids for the sake of their structural pattern as well as their biological and pharmacological potential. And for the fact that they are the obligate intermediates in flavonoid biosynthesis.

Flavanones have a chemical structure based on a C6-C3-C6 configuration consisting of two aromatic rings linked by a three-carbon chain. Flavanones present the structural feature of chirality, which distinguishes them from most classes of flavonoids. [36] Their stereogenic centre (chiral centre) is located at C-2 so they are often optically active. [35] Flavanones are generally glycosylated by a disaccharide at position seven: either a neohesperidoside, which imparts a bitter taste (such as to naringin in grapefruit) or a rutinose, which is flavourless. [14] **Table1.9**

Table1.9 Flavanones Basic Structure and Examples [29]



Position Compound	5	7	3’	4’
Naringenin	OH	OH	-	OH
Naringin	OH	*O*-Rha-Glu	-	OH

Hesperetin	OH	OH	OH	OCH_3
Hesperidin	OH	*O*-Rha-Glu	OH	OCH_3

Flavanones are present in citrus fruits, cherries, grapefruits, and tomatoes.[37] along with the hand-squeezed or industrially processed juices from fresh fruits.[36] Flavanones can also be found in certain aromatic plants such as mint, but mainly they are present in high concentrations only in citrus fruit.[14] such as sweet (Citrus sinensis) and sour oranges (C. aurantium) and their near relatives—tangerines/mandarins (C. reticulata), tangors and tangelos.[38] The solid parts of citrus fruit, particularly the albedo and the membranes separating the segments, have a very high flavanone content, the whole fruit may contain up to five times as much as a glass of orange juice. [14]

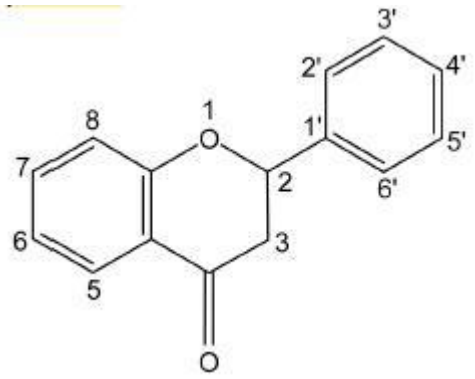
Natural flavanones are reported to exhibit numerous promising biological activities and pharmacological activities. [35] As mentioned Flavanoes are mostly located in the albedo which makes them the second barrier against pathogen attack, before flavones that are located in the outermost shell of the fruit, the flavedo. Flavanones show strong antioxidant and radical scavenging activity, and appear to be associated with a reduced risk of certain chronic diseases, the prevention of some cardiovascular disorders, and certain kinds of cancer. Flavanones also exhibit antiviral, antimicrobial, and anti-inflammatory activities, beneficial effects on capillary fragility, and an ability to inhibit human platelet aggregation, anti-ulcer and anti-allergenic properties. [36]

5.1.3 Flavones

The flavones are important members of the flavonoid family. They are natural products of the benzopyran class, constituting an important group of oxygen heterocycles that are widely distributed in the plant kingdom as secondary metabolites. [39] Flavones have three functional groups, including hydroxy, carbonyl, and conjugated double bond; consequently, they give typical reactions of all three functional groups. Flavones are colorless-to yellow crystalline substances, soluble in water and ethanol. They give a yellow color solution when dissolving in alkali. Flavones are moderate-to-strong oxygen bases and are soluble in acids due to the formation of oxonium salts having pKA values ranging from 0.8-2.45. [28] Flavones are lipophilic as well as hydrophilic, having polar functionalities in different positions, and the skeleton itself is amenable for generation

of functionalities for selective modulation of different enzymes. [39] Flavone has a three-ring skeleton C6-C3-C6, and the rings are referred to as A-, C-, and B-rings, respectively. [28] **Table1.10**

Table1.10 Flavones Basic Structure and Examples [29]



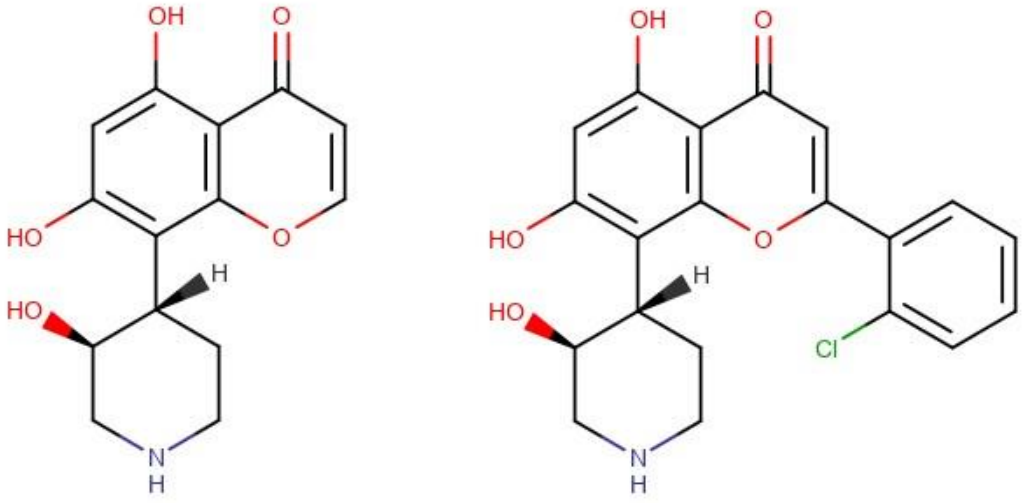
Position Compound	5	7	3’	4’
Apigenin	OH	OH	-	OH
Luteolin	OH	OH	OH	OH
Chrysin	OH	OH	-	-

Flavones have a widespread presence in the majority of fruits and vegetables. [39] They are also found in Medical herbs and cereals. [37] Important sources of flavones are parsley and celery. Cereals such as millet and wheat contain C-glycosides of flavones. Large quantities of polymethoxylated flavones: tangeretin, nobiletin, and sinensetin (up to 6.5 g L/1 of essential oil of mandarin) have been identified on the skin of citrus fruit. **Table1.11 [**14]

Table1.11 Flavones Content in Foods

Flavones	Source	Content by wt or vol mg kg^{-1} fresh wt (or mg L^{-1})
Apigenin	Celery	20–140
Luteolin	Capsicum pepper	5–10

Flavones are well known for their antioxidant activity; recent studies have shown the positive effect of flavones on diseases related to oxidative stress. Due to the wide range of biological activities of flavones, their structure–activity relationships have generated interest among medicinal chemists, and this has culminated into the discovery of the clinical anticancer agent flavopiridol, as well as several lead molecules in other disease areas. Flavopiridol is synthetic flavone, structurally related to the natural alkaloid rohitukine **Figure1.3**, originally purified from Dysoxylum binectariferum, a plant indigenous to India and used in its folk medicine. Flavones are also known for their ability to modulate several enzyme systems. [39] [40] As well as their positive effect on diseases related to oxidative stress, such as atherosclerosis, diabetes, cancer, Alzheimer's disease, etc. Flavones have been considerably explored. Various natural, semisynthetic and synthetic derivatives of flavones have been synthesized and evaluated for several therapeutic activities like anti-inflammatory, anti-oestrogenic, antimicrobial, anti-allergic, antioxidant, antitumor and cytotoxic activities. In addition, Flavones have anti-proliferative, acetylcholinesterase, activities and they are also used in cancer, cardiovascular disease and neurodegenerative disorders. [28] Regarding plants, flavones protect plants from UV radiation, attract insects for pollination and participate in interactions with soil microbes. [39]



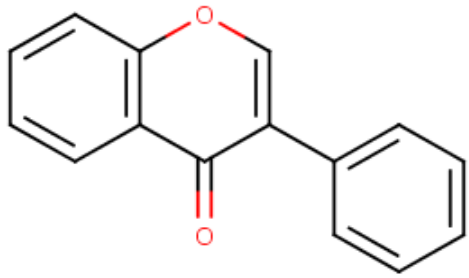
(a) **Rohitukine** (b) **Flavopiridol or Alvocidib**

Figure 1.3 Rohitukine and Flavopiridol (or Alvocidib) Structures

5.1.4 Isoflavones

Isoflavones are polyphenolic secondary plant metabolites that are produced primarily from members of the Leguminosae [41] and found in a variety of plants, and soybeans being the main source [14] hence, Isoflavones are regarded as protective components of soybeans. Isoflavone metabolism and bioavailability are key to understanding their biological effects. [42] Over the past years, hundreds of naturally occurring isoflavones have been isolated and identified. All isoflavones share the 3-phenylchromen-4-one backbone [41] and have their Ring B attached to the C3 position of Ring C. [18] **Table 1.12** Annex Twelve different isoflavones were detected in soybeans [43] and red clovers, the main ones being Genistein and Daidzein along with Glycetein, Biochanin A and Formononetin. All these isoflavone aglycones are mostly found as 7-O-glucosides and 6'-O-malonyl-7-O-glucosides. [16] [18]

Table 1.12 Isoflavones Basic Structure and Examples [41]



Biochanin A	OH	H	OH	H	H	OCH_3	H
Daidzein	H	H	OH	H	H	OH	H
Formononetin	H	H	OH	H	H	OCH_3	H
Genistein	OH	H	OH	H	H	OH	H
Glycitein	H	OCH_3	OH	H	H	OH	H

Since beans, particularly soybean are a major part of the diet in many cultures [18] it could be stated that isoflavones are part of the human diet all over the world. [41] As previously indicated

Isoflavones occur in a range of plants, particularly those in the Leguminosae family, such as soya (Glycine max) and medicinal plants such as red clover (Trifolium pratense) [44] and kudzu (Pueraria lobata). In addition, isoflavone-rich extracts of soy, red clover, and kudzu root are used in dietary supplements. [41] Isoflavones can also be found in soymilk, nuts, tofu and miso (Japanese soup). [37] The isoflavone content of soya and its manufactured products varies greatly as a function of geographic zone, growing conditions, and processing. Soybeans contain between 580 and 3800 mg isoflavones in 1 kg fresh weight, and soymilk contains between 30 and 175 mg/L. [14] [16]

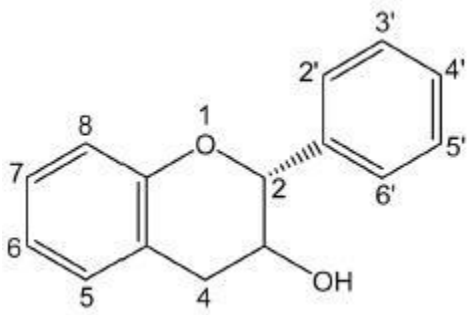
Isoflavones demonstrate superior effect on human health [16]. They have been extensively investigated and display a myriad of pharmacological activities that have been supported by clinical and epidemiological studies, particularly estrogenic effects, as well as for anti-inflammatory properties. Soya isoflavones such as genistein have been associated with potential health benefits in relation to metabolic disorders such as diabetes. Genistein may inhibit inflammation to ameliorate the endothelial dysfunction implicated in insulin resistance [44]. Many potential health benefits of isoflavones from soy products have been investigated, including effects on cancer, vascular disease, osteoporosis, and menopausal symptoms. Because of the purported beneficial effects, use of soy products and soy based supplements has increased significantly. The approval by the U.S. Food and Drug Administration (1999) relating the consumption of soy products with the alleviation of cardiovascular disease resulted in increased attention to soy isoflavones in recent years. [43] However, apart from putative beneficial health effects, the consumption of high doses of isoflavones has also raised concerns about their safety. [41]

5.1.5 Flavanols

Flavanols, otherwise called as flavan-3-ols, are a subclass of flavonoids as well as being a family of bioactive compounds although their bioavailability rests on many elements such as food processing, cooking, digestion, biotransformation, absorption and metabolism. [30] [45] Flavanols, like most other flavonoids, exist in plasma predominantly in their conjugated forms. [46] Flavanols are present in a wide range of botanical sources as both monomer form (catechins) and the polymer form (proanthocyanidins).[14] Flavanol monomers are (–)-epicatechin and (+)-catechin, and procyanidins are oligomers of epicatechin and catechin. Unlike other classes of flavonoids, which exist in plants primarily in glucoside forms, flavanols are usually present in the aglycone form as monomers, oligomers or esterified with gallic acid [30] **Table1.13.** Monomeric

flavanols or catechins are characterized by having a C6-C3-C6 skeleton with a hydroxyl group in position three of the C-ring. Furthermore, flavanols represent the largest class of monomeric C6-C3-C6 flavanols. Along with catechin and epicatechin being out of the commonest flavonoids known. [47]

Table1.13 Flavanols Basic Structure and Examples [29]



Position Compound	3	5	7	3’	4’	5’
(+)-Catechin	βOH	OH	OH	OH	OH	-
(–)-Epicatechin	αOH	OH	OH	OH	OH	-
(–)-Epigallocatechin	αOH	OH	OH	OH	OH	OH

Flavanols can be found in common foodstuffs as well as in herbal remedies, and dairy products [46] but flavanols are mainly present in fruits and derived products like fruit juices or jams and cereals **Table 1.14** the rest is summarized in the Annex. The richest sources of flavanols include cocoa, red wine, green tea, red grapes, berries and apples. [30] Cocoa contains particularly high quantities of flavanols. [45] The latter is also present up to 300 mg L/1 in red wine and 200 mg in green tea whereas for apples latest research reveals that flavanols are the major polyphenols in apples, accounting for 65–85% of total polyphenol contents in the dessert and cider varieties analysed. [14] On the other hand flavanols are practically non-existent in vegetables and legumes, with the rare exception of lentils and broad beans. Flavanols are often present in the peels or seeds of fruits and vegetables. [47] Catechin and epicatechin are the main flavanols in fruit, whereas

gallocatechin, epigallocatechin, and epigallocatechin gallate are found in certain seeds of leguminous plants, in grapes, and more importantly in tea. [14] Flavanols content in food can be affected by many factors such as environmental, food processing, and food storage conditions. Higher flavanol levels generally appear in fresh fruits than in either dried or cooked fruits, and in some cases environmental variation can explain large flavanols content disparity within species. [46]

Table 1.14 Flavanols in Fruits and Berries. [31]

Fruit	Flavanols (mg/100 g fresh weight)
Cherry	6.3–23
Custard apple	18–25
Plum	3.7–79
Strawberry tree fruit	10–29

Flavanol are not only present in beverages, fruits and vegetables, food grains, herbal remedies, dietary supplements, and dairy products as stated above, but they're are also considered as functional ingredients and have been reported to exhibit several health beneficial effects by acting as anticarcinogen,cardiac preventive, antimicrobial, anti-viral, and neuroprotective agent ,and may play a significant role in maintaining neurological health. [46] Flavanols are also potent antioxidants, scavenging free radicals in vitro and in vivo. While some of the actions of flavanols can be linked to antioxidant activities, other modes of action may also occur, including modulation of intracellular signaling, effects on membrane fluidity and regulation of cytokine release or action [30] Flavanols also have direct effects on cerebral blood flow. In one study, cerebral blood flow was enhanced for as long as four hours after a single dose of high-flavanol cacao. These studies highlight the possibility that central effects of flavanols may be neuroprotective, which may serve to lessen the likelihood of vascular depression. [45] They also have an effect on food quality parameters such as astringency, bitterness, sourness, sweetness, salivary viscosity, aroma, and color formation. And have the ability to aid food functionality in terms of microbial stability, foamability, oxidative stability, and heat stability. not only that but flavanols also have the ability to chelate metals such as iron and other essential minerals and reportedly limits growth of invasive

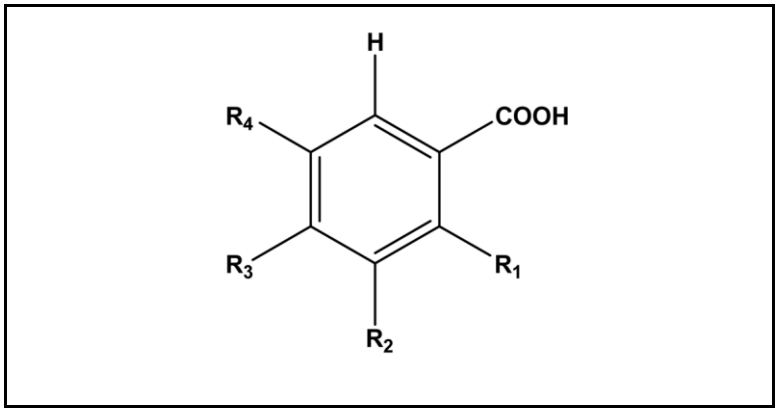
microorganisms by causing severe essential mineral-depletion as has been documented in bacteria. The presence of (–)-epicatechin in plant tissue may also provide a similar resistance against fungal attack. Flavanol have also been implicated in a plant's ability to tolerate high lead levels, as Today, the generally accepted biological role of flavanol in plants relates to their protection against harmful intruders such as microbes, fungi, insects and herbivorous animals. Despite what has been previously mentioned there is also evidence that indicate the contrary and states that flavanol may also behave as anti-nutrients, procarcinogens, pro-oxidants, hemorrhage inducers, mutagens or hepatotoxins depending on the source, type, quantity and existence of other dietary burdening factors. [46]

5.2 Non-Flavonoids

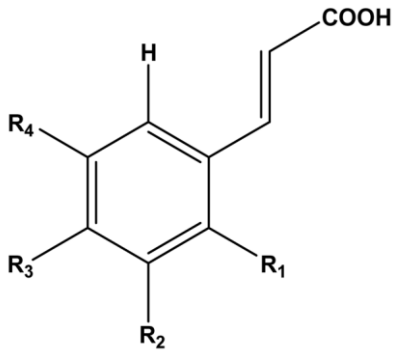
5.2.1 Phenolic Acids

Phenolic acids are aromatic secondary plant metabolites widely distributed throughout the plant kingdom. [29] [48] The term “phenolic acids”, in general, designates phenols that possess one carboxylic acid functionality. [29] Phenolic acids can be divided into two major groups, depending on their structure [49]; hydroxybenzoic acids and hydroxycinnamic acids, which are derived from non-phenolic molecules of benzoic and cinnamic acid, respectively. Chemically, these compounds have at least one aromatic ring in which at least one hydrogen is substituted by a hydroxyl group. The most frequently encountered and studied phenolic acids are caffeic and ferulic acids. [50] These naturally occurring phenolic acids contain two distinctive carbon frameworks: the hydroxycinnamic and hydroxybenzoic structures **Table 1.15**. Although the basic skeleton remains the same, the numbers and positions of the hydroxyl groups on the aromatic ring make the difference and establish the variety. [29]

Table 1.15 Structure of the Most Common Natural Phenolic Acids. [29]



Hydroxybenzoic Acids				
Name	R1	R1	R3	R4
Benzoic acid	H	H	H	H
p-Hydroxybenzoic acid	H	H	OH	H
Vanillic acid	H	OCH_3	OH	H
Gallic acid	H	OH	OH	OH
Protocatechuic acid	H	OH	OH	H
Syringic acid	H	OCH_3	OH	OCH_3
Gentisic acid	OH	H	H	OH
Veratric acid	H	OCH_3	OCH_3	H
Salicylic acid	OH	H	H	H



Hydroxycinnamic Acids

Name	R1	R1	R3	R4

Cinnamic acid	H	H	H	H
o-Coumaric acid	OH	H	H	H
m-Coumaric acid	H	OH	H	H
p-Coumaric acid	H	H	OH	H
Ferulic acid	H	OCH_3	OH	H
Sinapic acid	H	OCH_3	OH	OCH_3
Caffeic acid	H	OH	OH	H

Phenolics have an array of health-promoting benefits; they are of current interest due to their important biological and pharmacological properties, especially the anti-inflammatory, antioxidant, and antimutagenic and anticarcinogenic activities [29] as well as for their roles in food quality and their organoleptic properties, potential protective role, through ingestion of fruits and vegetables, against oxidative damage diseases such as coronary heart disease, stroke, and cancers.[48] Since they are widespread in plant-based foods, humans consume phenolic acids on a daily basis. The estimated range of consumption is 25 mg to 1 g a day, depending on diet. They can be found in fruit, vegetables, grains, teas, coffees, spices, etc. [29] [50] [51]

5.2.2 Stilbenes

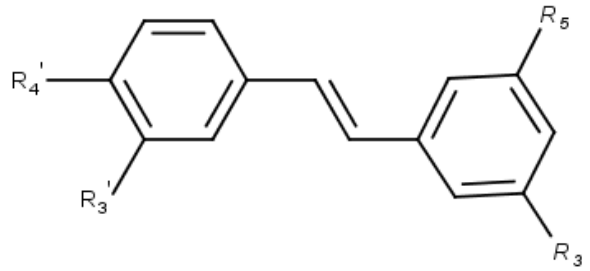
Stilbenes are a small family of plant secondary metabolites derived from non-flavonoid phytochemicals [52] and produced in a number of unrelated plant species. However, stilbenes do not have a wide distribution in the plant kingdom, [53] therefore, their presence in the human diet is limited to a few foods such as grapes, red wine, peanuts and some types of berries. [54]

The complex structure and diverse biological activities of Stilbenes have aroused great interest. These compounds and their derivatives are of great significance in drug research and development [53] and have many effects on plant disease resistance and human health. [55] Stilbenes have an extraordinary potential for the prevention and treatment of different diseases, including cancer, due to their antioxidant, cell death activation, anti melanogenesis and

chemoprevention, and anti-inflammatory properties which associate with low toxicity under in vivo conditions. [52] [56]

The stilbene structure is based on the C6–C2–C6 backbone, defined by two aromatic rings linked by an ethylene bridge. The most described in the literature and best-characterized stilbene is resveratrol **Table 1.16**. [54] [57] More than 400 stilbene derivatives have been identified. Their structures range from monomers to octamers and carry various substituents at different positions, like glycosyl, hydroxyl, methyl or isopropyl groups. [53] [54]

Table 1.16 Structure of the Most Common Natural Stilbenes. [57]



Stilbenes

Name	R3	R3’	R4’	R5
Resveratrol	OH	H	OH	OH
Piceatannol	OH	OH	OH	OH
Pinosylvin	OH	H	H	OH

5.2.3 Tannins

Tannins derived from the French ‘tanin’ [58] commonly referred to as tannic acid [59] are water-soluble macromolecular phenolic compounds derived from secondary metabolites in higher plants. They differ from most other phenolic compounds in their ability to precipitate protein and other macromolecules in solution. [58] [60] Important sources for Tannins are found in a variety of plants utilized as food and feed. such as sorghum, millets, barley, dry beans, fava beans, peas, carobs, pigeon peas, winged beans, and other legumes. Fruits like apples, bananas, blackberries, cranberries, dates, grapes, hawthorn, peaches, pears, persimmons, plums, raspberries, and strawberries also contain an appreciable quantity of tannins. [59]

Tannins have a wide application in breweries and in the cosmetics, pharmaceutical, chemical and food industries. [60] As a result of attracting scientific interest, owing to their antiviral, antibacterial, and especially antitumor activity. For example, certain tannins can selectively inhibit HIV replication. [58] In addition to their unique ability to convert animal skin into leather. [59] Above all, they are known for their antinutritional effects where they cause a reduction in nutrient absorption due to the formation of complexes with proteins, and to a lesser degree with metal ions, amino acids, and polysaccharides. Which means Tannins have negative effects on animal nutrition making them indigestible. [60] Therefore, foods rich in tannins are considered to be of low nutritional value, [59] which leads to lower involuntary consumption, efficiency in digestibility and animal productivity. However, studies have shown that in ruminants, lower tannin concentrations in feed led to increased nitrogen assimilation, resulting in higher growth rates and milk production. [60]

Tannins can be classified into two groups: hydrolyzable and condensed tannins. This latter includes Non-hydrolysable oligomeric and polymeric proanthocyanidins and they are more resistant to microbial degradation than hydrolyzable tannins and can be soluble in aqueous organic solvents, depending on their structure. Whereas for hydrolysable tannins they include both the gallotannins and the ellagitannins **Figure 1.4**. [58] [59] [60]

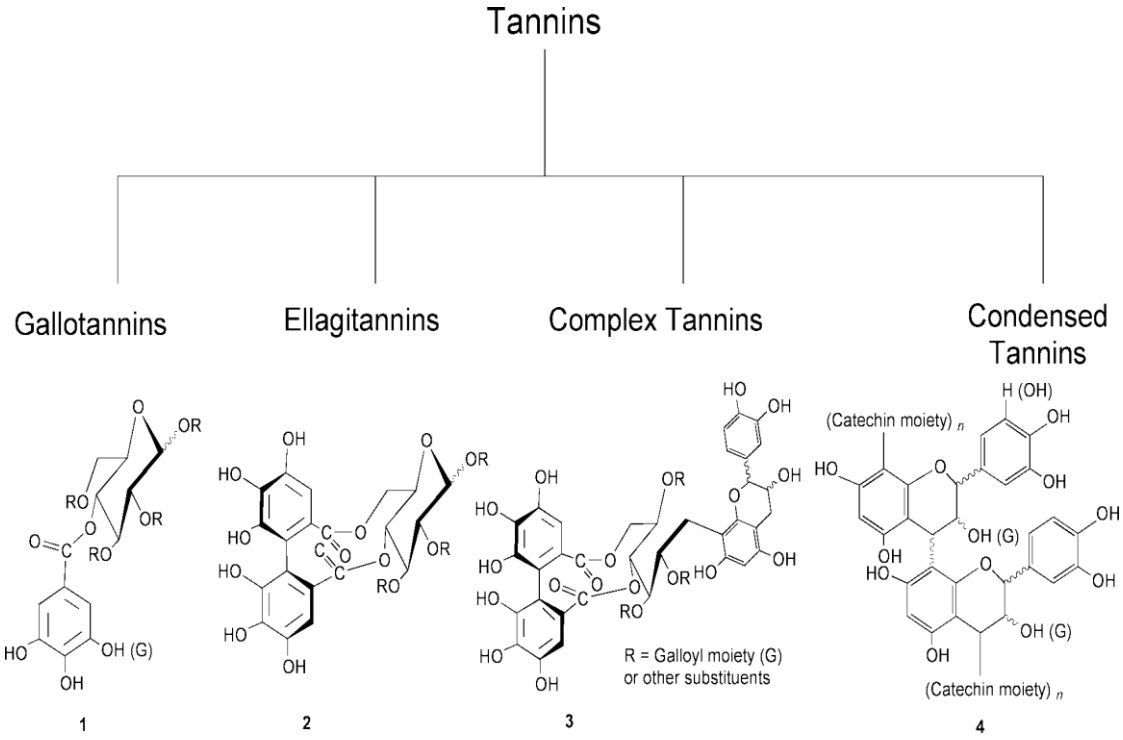


Figure 1.4 Classification of the Tannins. [48]

5.2.4 lignans

Lignans are diphenolic plant compounds which are one of the three main plant compounds classified as phytoestrogens and the other two are isoflavonoids and coumestans. [61] The phytoestrogen family is known for its health properties. [61] Lignans, as natural products, are distributed widely in the plant kingdom. [62] More than 200 compounds in this general class have been identified [63] therefore they are usually present in the human diet. [61] Especially in the western world diets where they are present in high concentrations in flaxseed and other seeds, as well as in fruits and vegetables. As well as in, beverages such as coffee, tea, and wine [64] Dietary lignans are related to fiber polyphenols; therefore they are present at considerable concentrations in fiber-rich foods, including grains such as wheat, barley, and oats; the concentration is slightly reduced in nuts and oilseeds, cereals and bread, legumes such as beans, lentils and soybeans, fruits, vegetables such as garlic, asparagus, broccoli and carrots, soy products, meat products and other processed foods, alcoholic and non-alcoholic beverages [64] Lignans are also found in roots, rhizomes, stems, leaves, seeds and. With some exceptions, these sources do not provide commercially useful quantities. [65]

It is generally believed that the intake of lignan rich foods is part of a healthy diet, Lignans have been associated with several health properties such as protection against LDL oxidation and inhibition of cancerous cell growth in skin, breast, prostate, colon and lung tissues. Due to their chemical structures being similar to oestrogen, they could act as hormonal modulators in breast cancers through oestrogenic or antiestrogenic activities. Clinical trials have reported a reduction in the risk of postmenopausal breast cancer, there are also reports that indicate the correlation between the decreased growth of breast cancer and women who consume flaxseeds daily. [62]

According to reports 56 lignans have antioxidative activity, 48 have anticancer properties. 34 plant lignans were found to have anti-inflammatory activity, whereas reports of antimicrobial activity (11 lignans) and immunosuppressive activity (5 lignans). [65] Additionally, lignans are known to have anti-tumour, antimitotic and antiviral activity and to specifically inhibit certain enzymes. Also toxicity to fungi, insects and vertebrates is observed for some lignans and a variety of physiological activities have been documented. There is also evidence that lignans play a role in plant-fungus, and plant-insect interactions. [63] They probably play an important role in plant defense against various biological pathogens and pests. On top of that, they may participate in plant growth and development. Lignans also have important pharmacological activities, including

antitumor, anti-inflammatory, immunosuppressive, cardiovascular, antioxidant and antiviral actions. Regarding the chemical structure, lignans show an enormous structural diversity, their molecular backbone consists only of two phenylpropane (C6–C3) units. **Figure 1.5** [65]

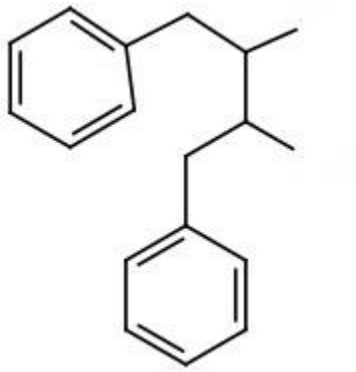
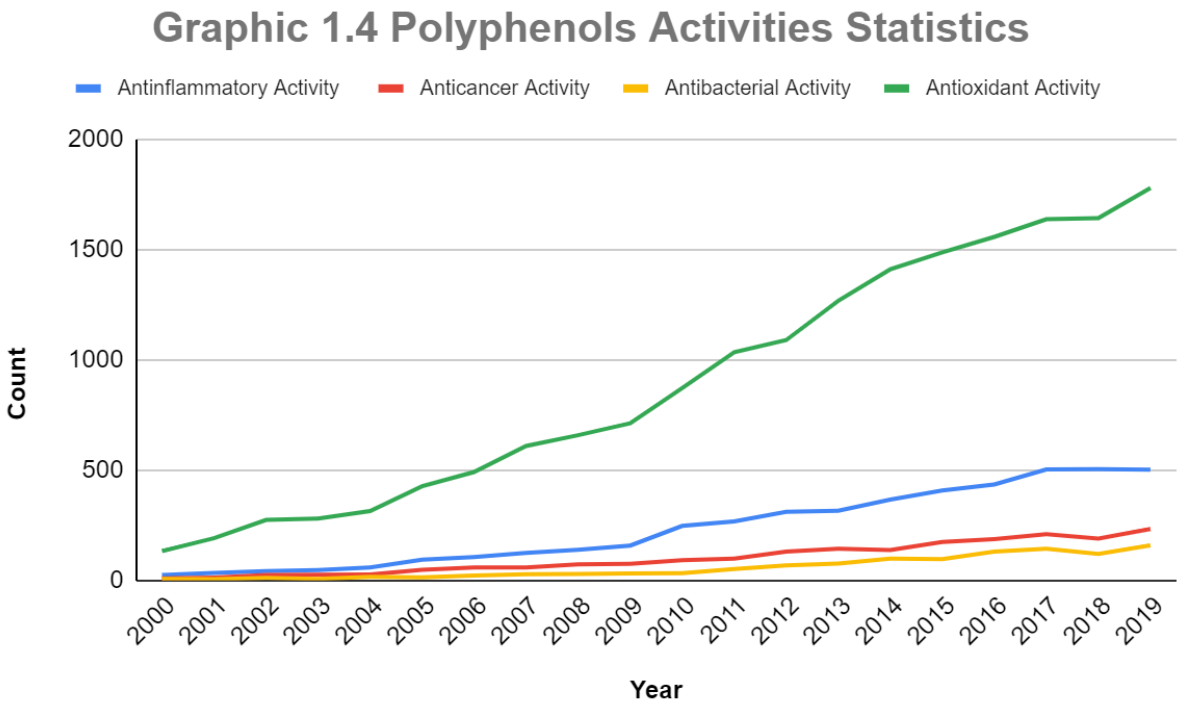


Figure 1.5 The Basic Structure of Lignans [66].

6. Activities of Polyphenols

6.1 PubMed Polyphenols Activities Trends

Because of their safety and therapeutic potential, plant-derived functional foods are getting considerable attention [16]. Notably, phytochemicals and their various provided bioactivities have received special notice in the last decade, especially Polyphenols representing the most abundant group of phytochemicals. It is well known that polyphenols exhibit anti-inflammatory activity as antioxidant, anti-inflammatory, anti-cancer variables and potent biological properties relies on their structure, which defines their stability.their permeability or their affinity with their target such as plasma membrane, enzymes or DNA.[67] [68] [69] [70] These various biological activities increased the interest of the scientific community, the growth of this interest is translated in the number of scientific studies. According to statistics, antioxidant, anti-inflammatory, anticancer and antimicrobial respectively are the most known and studied activities since 2000 up to now. [71] Graphic **1.4** illustrates the result of a PubMed search with the keywords "anti-inflammatory/anticancer/antibacterial/antioxidant activity of polyphenols" in the previous twenty years. As seen, the antioxidant activity is the most studied. It researched 1642 articles published in 2018 and 1779 in 2019.



6.2 Anti-Inflammatory Activity

Inflammation is an immunological defense mechanism by which the body fights the presence of a biological, chemical or physical agents [68]. As defined firstly by the Roman physician 'Aurelius Cornelius' [70]: Redness, heat, swelling and pain are in fact, the four major inflammatory characteristics that transpire at the site of a wound due to the widening of the blood vessels to enable the entry of specific white blood cells. [72] In the meantime, the immune system procedure is executed by the training and development of immune cytokines, the launch of reactive oxygen species (ROS), reactive nitrogen species (RNS), and proinflammatory cytokines to eliminate foreign microorganisms and the rebuild of damaged tissue [68] [73], however their overproduction, might lead to the occurrence of several chronic diseases involving cancer, diabetes type II, obesity, arthritis, neurodegenerative diseases, and cardiovascular diseases [74]. Increased inflammatory response and greater oxidative stress burden are two of the main pathogenic mechanisms responsible for neurodegenerative diseases which represent a major cause of morbidity of the working force throughout the world and are better known as the 'King of Human Miseries'. [68] [75] The increased inflammatory response is also the major cause of the pandemic COVID19 morbidity. Since the early 1970s, it has become very important to slow down the

inflammation process; non-steroidal anti-inflammatory drugs (NSAIDs) are treatments that are widely used to relieve pain and reduce inflammation. [74]

A variety of phytochemical classes have been linked to a vast array of mechanistic effects targeting inflammatory processes. [70] They began to receive considerable public attention due to their anti-inflammatory properties and therapeutic benefits in 1983. In fact, 12 out of the 40 anti-inflammatory drugs were derived from or based on these natural products as shown in **Table 1.17** (the rest is summarized in the annex). Thus, those latter phenolic acids can be regarded as an alternative rational method to inflammatory curing diseases or management [68] [76] [77]. Moreover, researches have also shown that populations consuming foods that are high in specific polyphenols have a reduced risk of inflammatory disease.

Table 1.17 Anti-inflammatory Activities of Some Phenolic Compounds [69]

Phenolic compounds	Anti-inflammatory activities
Apigenin	Inhibiting LPS-induced inflammation
Catechin	Against monosodium urate-induced inflammation
Epigallocatechin gallate	Suppressing melanoma growth
Ellagic acid	Ameliorating monocrotaline -induced pulmonary artery hypertension
Green tea	Decreasing PCB 126 induced oxidative stress

Although the underlying mechanism of this anti-inflammatory activity is not clearly understood, in contrast there is a correlation between high food intake rich in these compounds and inflammatory response expression level. [76] The association of phenolic structure and anti-inflammatory activity has been observed and structural requirements have been established using different targets of inflammation. In this sense, a planar ring system is essential in the flavonoid molecules to exhibit this activity. Unsaturation in the C ring gives stability to the intermediate

radical species by resonance. Hydroxyl groups in B ring and at C5 and C7 of A ring are necessary, plus the number and position of hydroxyl groups as the catechol group at ring B, whereas the methylation of the hydroxyl groups at 3, 5, or 4' positions improved the activity and reduced the cytotoxicity. [68] Certain polyphenols exert their effects on the balance between pro- and anti-inflammatory cytokines production. Cytokines, the major mediators of local and intercellular communications in immune and inflammatory processes, were modulated by polyphenols; they are thought to be an important parameter in immune response homeostasis and inflammation underlining many diseases. [69] In vivo and in vitro studies demonstrate that polyphenols affect macrophages by inhibiting multiple key regulators of inflammatory response. Macrophages play the main role in the inflammatory response. [74]

6.3 Antibacterial Activity

One of the greatest medical achievements of the 20th century was the discovery of antibiotics. Unfortunately, their extensive, disproportionate, and unacceptable use has resulted in the selection and proliferation of resistant bacterial strains and a significantly increased ratio of treatment failure. Bacteria have developed several different resistance mechanisms, such as modification of the antibiotic binding site. Development of enzymes that can kill or modify the antibiotic structure. Mutations in genes that encode transportation proteins that cause disruption of the permeability of the cell wall and vigorous pumping out of antibiotic molecules. Because the production and introduction of a new antimicrobial drug is a complex, time-consuming, and very costly process and the production of resistance mechanisms by bacteria is swift and virtually boundless. Thus, the quest for and introduction of natural substances that can enhance the antibacterial efficacy of traditional antibiotics is the promising alternative in the ongoing fight against multi-drug resistant bacterial strains. It has been reported that plant-derived polyphenolic compounds such as flavonoids or phenolic acids exhibit antimicrobial properties against a large range of microorganisms, sensitize multidrug resistance strains to bactericidal or bacteriostatic antibiotics and are promising arms in the Weapon of Human Antimicrobials. Enhancing the antibacterial action of antibiotics may be described by natural compounds such as multi-target action where each compound works at a different location in the bacterial cell pharmacokinetic or physicochemical properties such as enhanced solubility or antibiotic bioavailability, or unique bacterial resistance mechanisms. [78]

It has been shown that polyphenols known to be synthesized by plants in response to microbial infection possess a broad spectrum of antibacterial effects against a large variety of microorganisms and a number of successful drugs have been developed against them. These antimicrobial agents may be classified as the agents that can either be bactericidal, killing bacteria, or bacteriostatic, slowing bacterial growth. [79] They can also act as bacterial growth activators, inhibitors, proteases, bacterial adhesives and protein transporters depending on their chemical structure (substitutions in the phenolic ring) and concentration. [80] Moreover, scientists explained this activity by the modification in the permeability of cell membranes, the changes in various intracellular functions induced by hydrogen binding of the phenolic compounds to enzymes or by the modification of the cell wall rigidity with integrity losses due to different interactions with the cell membrane.[81] [82] The effects of phenolic compounds were highly heterogeneous ranging from bacterial growth stimulation to antibacterial activity and depended on bacterial strains. [83]

Flavonoids are among the polyphenols with the highest spectrum of antimicrobial activity in relation to others. In particular, hydrophobic substituents such as prenyl groups. [84] In addition, they were suggested for exercising their antibacterial effects in three ways: direct bacterial killing, synergistic antibiotic activation, and bacterial pathogenic attenuation.[83] Polyphenols are capable of interacting with bacterial cell wall components and the bacterial cell membrane can prevent and control the formation of biofilms, as well as inhibit microbial enzymes, interfere in protein regulation, and deprive bacterial cell enzymes of substrates and metal ions.[85] As a result, the rise in the lipophilic character of phenolic compounds raises their antimicrobial activity by facilitating their interaction with the cell membrane, which can inflict permanent damage to the cytoplasmic membrane and cell material coagulation, which can also inhibit intracellular enzymes.[82] Gram-positive bacteria are commonly considered to be more sensitive to the phenolics naturally found in plant extracts than Gram-negative microbes. In vitro, disk diffusion technique in agar medium or disk solution is also a qualitative approach used to determine the efficacy of antibacterial activity extracts. [86] [87]

6.4 Anticancer Activity

Cancer is regarded as the "Emperor of all diseases" with the world's second-highest mortality rates.[88] Cancer cells invade or reach the adjacent healthy tissues of the body through the bloodstream and lymphatic systems, playing a direct or indirect role in the establishment and expression of the malignant phenotype and in its growth over time and space.[89] [90] The

existing traditional cancer therapies including chemotherapy, radiation therapy, hormone therapy, immunotherapy, and so on lack of precision and have significant side effects. They can attack healthy cells that are not direct chemotherapy or irradiation targets. Hence, phytochemicals have been considered for cancer treatment in the past two decades as they are natural, non-toxic, pharmacological agents and show differential response to cancer cells. [90] The use of phytochemicals as an important alternative to traditional cancer treatment because of their low side effects. The chemopreventive function of phytochemicals was linked to the modulation of various signaling cascades. Moreover, various phytochemicals were found to target the stem cells of cancer and to increase their sensitivity to chemotherapeutic drugs. [88] Polyphenolic phytochemicals are among the different types of isoflavones, curcumin, resveratrol and nimbolide, which have demonstrated their ability to minimize aggressive cancer properties through interaction with cellular signal conversion pathways that regulate the cell cycle wherein the protein kinase plays a key role in signaling cascades, regulating DNA transcription, gene expression in response to specific stimuli, tumor growth, and ability to survive. [88] [91] [92]

A common theory is that dietary polyphenols are anticarcinogens due to their antioxidant properties and this is primarily due to two main actions: first of all, there is a shift in the redox state, which is a cascade of redox reactions, in the cell or in a given tissue and a direct electron flux is transmitted by polyphenols which can then act as antioxidants or pro-oxidants. Second behavior is characterized by cellular function interference. The polyphenol has an inhibitory effect on the growth and proliferation of cancer cells. [91] [92] Oxidative stress is one of the most important and well-studied activities that produces the factors that contribute to the onset and development of the tumour. Polyphenols have the ability to prevent oxidative stress damage and they exert some of their biological effects via chromatin remodelling and other epigenetic modifications. [93] [94] [95] Natural polyphenols can be used to sensitize tumor cells to chemotherapy and radiotherapy by inhibiting mechanisms that contribute to resistance to treatment and combinations of two or three polyphenols have proven more effective in inhibiting cancer growth than single-compound treatments. [91] [96]

7. Antioxidant Activity

In various ways the term 'antioxidant' is definable. The word "against oxidation" also simply means any substance that, when present at low concentrations compared to an oxidizable

substrate that contains almost everything found in living cells, including proteins, lipids, carbohydrates and DNA, thus greatly slows or prevents the oxidation of the substrate. [97] The term antioxidant was originally used explicitly to refer to a compound that prevented oxygen intake. Therefore, it was the discovery of vitamins A, C and E as antioxidants that revolutionized the field and contributed to the realization of antioxidants significance in the biochemistry of living organisms. [98] Historically, gum guaiac was the first antioxidant allowed in the 1930s to stabilize animal fats, particularly lard. [8] Antioxidants are compounds which are stable enough to contribute and neutralize the electron to a free radical, which reduces its ability to damage. Such antioxidants mainly postpone or prevent cell damage through their free radical scavenging properties. Antioxidants can interact safely with free radicals and prevent chain reactions before big molecules are affected. Radical scavengers, hydrogen donors, electron donors, peroxide decomposers, singlet oxygen quenchers, enzyme inhibitors, synergists and metal chelating agents serve as antioxidants. [98]

In the past few years, antioxidant activity has been considered as an indicator of foodstuff healthfulness. Therefore, much attention has been paid to the antioxidant properties of polyphenols. Polyphenols are multifunctional and can act as reducing agents and free radical scavengers by hydroxyl radicals (´OH); free radicals are atoms, molecules or ions with unpaired electrons in the outer shell and are chemically highly reactive. They can start a chain reaction which leads to oxidative stress. [99] Polyphenols can also act as superoxide anion (O2) and 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical. [100] Indeed the capacity of these compounds to scavenge free radicals and/or limit their formation has been accepted as the main mechanism through which they could counteract oxidative stress.Preventing oxidation in biological systems which may lead to cellular membrane dysfunction and DNA damage.[101] [102]

Polyphenols' antioxidant activity is specifically related to the number of OH-groups in their chain, with their structures. The scavenging activity of phenolic antioxidants has been known to be associated with phenolic O – H bond dissociation enthalpy (BDE), adiabatic ionization potential (IP), proton dissociation enthalpy (PDE), proton affinity (PA), and electron transfer enthalpy (ETE). Since then, theoretical methods, particularly the Density Functional Theory (DFT) method, have been used successfully to calculate physicochemical descriptors such as polyphenolic compounds BDE and IP and to elucidate the structure-activity relationship (SAR) for phenolic antioxidants. [103] The efficacy of the antioxidant action depends fundamentally on the ease of

the transition of H-atom and the stability of the resulting radical phenoxy. The key determining factors, however, are the presence, number and relative location of additional phenolic hydroxyl groups, their involvement in the formation of intramolecular hydrogen bonds and the probability of conformationally dependent electronic delocalization in the largest part of the molecule. All of these factors affect the phenolic OH bond BDE: the weaker the homolytic cleavage of O:H bond, the easier it will be for the H-atom transmission. [8]

Phenolic antioxidants function as terminators of free radicals and metal ion chelators which can catalyze lipid peroxidation. Moreover, polyphenols interfere with the oxidation of lipids and other molecules by quick donation to radicals of a hydrogen atom to radicals. In addition, the phenoxy-radical intermediates are relatively stable; thus, a new chain reaction is not easily initiated. The phenoxy-radical intermediates could also act as propagation route terminators by reacting with other free radicals. Under certain conditions (high concentrations of phenolic antioxidants, high pH, presence of iron), however, phenolic antioxidants can initiate a process of auto oxidation and act like pro oxidant. Flavonoids are among the most potent antioxidants in plants, because they have one or more of the following structural elements of anti-radical activity; (1) an o-diphenolic group (in ring B), (2) a 2-3 double bond combined with a 4-oxo function, and (3) hydroxyl groups in positions 3 and 5. Quercetin is an example of one of the most common flavonols combining all these characteristics. [20]

Practical Framework

II. Chapter Methods and Materials

1. Antioxidant Activity Mechanisms

1.1 Enthalpy

Enthalpy (H) from the single Greek word, ενθαλπος (enthalpos), which means to warm within. [104] Enthalpy is the measure of the combination of internal energy E and the product of pressure P and volume V of a system. Thus $H = E + PV$. and $dH = dE + P\,dV$. For the change in enthalpy is related to the heat capacity at constant pressure,

$$(dH/dT)p = (dQ/dT)p = Cp$$

where dT is the change in temperature. The integration gives: $H = h0 + \int CP\,dT$ in which H_0 is a constant and T is temperature in absolute Kelvin units. [105]

1.2 Bond Dissociation Enthalpies

The making and breaking of bonds is the basis of all chemical transformations. Which is by definition the bond dissociation enthalpy of the molecules. [106] IUPAC defines bond-dissociation enthalpy (BDE) as the enthalpy (per mole) required to break a given bond of some specific molecular entity by homolysis. Homolysis is the cleavage of a bond in such a fashion that each resulting fragment retains one of the formerly bonded electrons. When a bond is created, energy is released because the bonded atoms are of lower energy level than the individual atoms. Thus, in order to break the bond, BDE energy must be provided to the molecule. As a matter of fact, the amount of energy required to break the bond is the same as that released upon the formation of the bond. BDE is expressed in either kJ/mol or kcal/mol. BDE is also dependent on the temperature and it is normally given for a temperature of 273.15K (25°C). The more stable a bond is the greater the amount of energy that is required to break it. As expected, different bonds exhibit different bond dissociation energies. [107]

The harmful action of free radicals (R*) can be avoided by scavenging them with flavonoids (FIOH) as shown in reaction (I).

$$FIOH + R^{\bullet} \rightarrow FIO^{\bullet} + RH \qquad \text{(I)}$$

The product of this reaction is flavonoid phenoxyl radical (Fl–O$^{\bullet}$). A higher stability of the radical (Fl–O$^{\bullet}$) corresponds to a better efficiency of the antioxidant (Fl–OH). It is assumed that conjugated hydrogen bonds in other words the resonance makes (Fl–O$^{\bullet}$) non-reactive (or less harmful).

This reaction could happen through at least three mechanisms:

1.3 Hydrogen-Atom Transfer (HAT)

As shown in reaction (II), this mechanism is characterized by the homolytic bond dissociation enthalpy (BDE) of OH group calculated as shown in equation (1)

$$FIOH \rightarrow FIO\bullet + H\bullet \qquad \text{(II)}$$

$$BDE = H(FIO\bullet) + H(H\bullet) - H(FIOH) \qquad (1)$$

H(Fl-O$^{\bullet}$) is the enthalpy of the flavonoid phenoxyl radical generated after H abstraction, *H*(H) is the enthalpy of the hydrogen atom and *H*(Fl–OH) is the enthalpy of the parent flavonoid molecule. A lower BDE value, usually related to a greater ability to donate a hydrogen atom from the hydroxyl group, results in an easier free radical scavenging reaction.

1.4 The Single Electron Transfer Followed by Proton Transfer (SET-PT)

This mechanism has two steps, firstly a Single Electron Transfer characterized by the Ionization Potential (IP) as shown in reaction (III) and equation (2) respectively.

$$FIOH \rightarrow FIOH^{\bullet+} + e^{-} \qquad \text{(III)}$$

$$IP = H(FIOH^{\bullet+}) + H(e) - H(FIOH) \qquad (2)$$

Secondly, a Proton Transfer characterized by the Proton Dissociation Enthalpy as shown in reaction (IV) and equation 3 respectively.

$$FIOH^{\bullet+} \rightarrow FIO^{\bullet} + H^{+} \qquad \text{(IV)}$$

$$PDE = H(FIOH^{\bullet}) + H(H^{+}) - H(FIOH^{\bullet+}) \qquad (3)$$

1.5 The Sequential Proton Loss Electron Transfer (SPLET)

This mechanism has two steps, firstly a deprotonation characterized by the Proton Affinity (PA) as shown in reaction (V) and equation (4) respectively.

$$FIOH \rightarrow FIO^{-} + H^{+} \qquad \text{(V)}$$

$$PA = H(FIO) + H(H^{+}) - H(FIOH) \qquad (4)$$

Secondly, an Electron Transfer characterized by the Electron Transfer Enthalpy as shown in reaction (VI) and equation 5 respectively.

$$FIO^- \rightarrow FIO^\bullet + e^- \quad \text{(VI)}$$

$$ETE = H(FIO^\bullet) + H(e) - H(FIO) \quad (5)$$

2. Experimental Antioxidant Activity Measurements

Various methods are used to investigate the antioxidant properties of samples such as foods, beverages, diets, plant extracts and commercial antioxidants. [108] These methods exist because antioxidant activity should not be concluded based on a single antioxidant test model. In addition to that, many in vitro test procedures are carried out for evaluating antioxidant activity. The diversity of these methods and tests leads researchers to critically verify methods of analysis before adopting one for their research purpose [109], this is necessary since the chosen method used has a major impact on the results.

There has been an ongoing debate about the methods and which one is best amongst them, [110] considering the extreme diversity they have shown. Some methods involve a distinct oxidation step followed by measurement of the outcome. [112] On top of that, antioxidants act by several mechanisms and one assay cannot capture the different modes of action of antioxidant. Therefore, it is prudent to use more than one type of antioxidant assay to measure antioxidant activities and to include at least one assay that has biological relevance. Some of these methods are: TLC Autography technique, Cellular antioxidant activity (CAA) assay, Dye-substrate oxidation method, Cupric Ion Reducing antioxidant capacity (CUPRAC), Cellular antioxidant activity,Enhanced chemiluminescence (ECL),DPPH (2,2-diphényl-1-picrylhydrazyl), Ferric-raducing antioxidant power (FRAP) assay , Total radical trapping antioxidant parameter (TRAP), Oxygen radical absorbing capacity (ORAC) assay j) Trolox equivalent antioxidant capacity (TEAC), ABTS{2,2' – azinobis-(3-ethyl-benzothiazoline- 6-sulphonic acid)} and Folin-Ciocalteu method.[110] The most commonly-used procedures for measuring antioxidant capacity are FRAP, ABTS, TEAC , DPPH and ORAC. [108]

2.1 DPPH

Numerous methods are available for the determination of antioxidant potential of different biological samples. However, a single method is not suitable for all. The DPPH is one of those available methods. [113] It was originally conceptualised by Blois (1958) [114] with the viewpoint to identify the antioxidant activity [113] with the use of 1,1-diphenyl-2-picrylhydrazyl (a,a-

diphenyl-bpicrylhydrazyl / $C_{18}H_{12}N_5O_6$) . This latter is characterized as a stable free radical by virtue of the delocalisation of the spare electron over the molecule as a whole **Figure 2.6** so that the molecule does not dimerize, As with most other free radicals. [109] [113] [115]

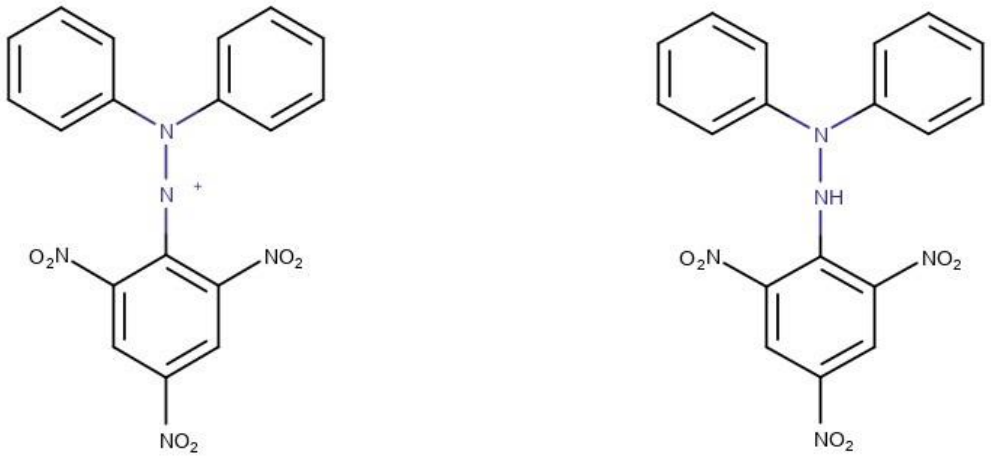


Figure 2.6 Diphenylpicrylhydrazyl (free radical) Diphenylpicrylhydrazine (non radical).

The DPPH method is frequently applied for assessment of free radical scavenging potential of an antioxidant molecule and considered as one of the main and colorimetric (the neutral molecule being purple whereas for the radical it is yellow) methods for the evaluation of antioxidant properties of pure compounds [114] suchlike wheat grain and bran, conjugated linoleic acids, herbs, edible seed oils, and flours in several different solvent systems including ethanol, aqueous acetone, methanol, aqueous alcohol and benzene. Furthermore, it is a convenient method for the antioxidant assay of cysteine, glutathione, ascorbic acid, tocopherol and polyhydroxy aromatic compounds, for olive oil, fruits, juices and wines, [113] [116] and different foods, beverages [108] and extracts, because the radical is stable and does not need to be generated as in other scavenging assays. The results are highly reproducible and comparable to other scavenging methods such as ABTS. [115] The method offers advantages of being rapid, simple, easy, accurate, sensitive, and inexpensive and provides firsthand information on the overall antioxidant capacity of the test system. It can adjust as well as being used to quantify antioxidants in complex biological systems for solid or liquid samples. [113]

This assay is based on the principle that DPPH on accepting a hydrogen atom from the scavenger molecule, also known as the antioxidant, leading into the reduction of DPPH to DPPH2,

the purple colour changes to yellow with concomitant decrease in absorbance at 515 nm. The colour change is monitored by spectrophotometrically and utilised for the determination of parameters for antioxidant properties. [114] Moreover, in order to evaluate the antioxidant potential and the change in optical density of DPPH radicals are tracked. The percentage of the DPPH radical scavenging is calculated using the equation given below:

$$\% \text{ inhibition of DPPH radical} = ([\text{ Abr} - \text{ Aar}] / \text{Abr}) * 100$$

where Abr is the absorbance before reaction and Aar is the absorbance after reaction has taken place. [109]

2.2 ABTS

The ABTS method is a colorimetric assay set on the ABTS cation radical formation. [115] The '2,2'-azino-bis 3-ethylbenzthiazoline-6-sulphonic acid'. This cation radical has a dark blue color [117] when it's neutral state is colorless. This latter absorbs at 743 nm and is formed by the loss of an electron by the nitrogen atom of ABTS. [118] The ABTS assay is an electron transfer-based assay [117] that stands on the inhibition of the absorbance of radical cation ABTS by antioxidants. [115] Generation of the ABTS radical cation forms the basis of one of the spectrophotometric methods that have been applied to the measurement of the total antioxidant activity of solutions of pure substances, aqueous mixtures, and beverages. [119]

The original ABTS assay revolved around the activation of metmyoglobin with hydrogen peroxide in the presence of ABTS to produce the radical cation in the presence or absence of antioxidants. Other antioxidants can also be used for oxidation of ABTS, including manganese dioxide potassium persulfate and horseradish peroxidase. This has been criticized on the basis that the faster reacting antioxidants might also contribute to the reduction of the ferryl myoglobin radical. A more appropriate format for the assay is a decolorization technique in which the radical is generated directly in a stable form prior to reaction with putative antioxidants. [117] [119] The improved technique for the ABTS is based on the ability of an antioxidant to stabilize the ABTS colored cation radical, which can be previously formed by the oxidation of ABTS by methemoglobin and hydrogen peroxide. The modified technique for the generation of the ABTS cation radical involves direct production of the green-blue ABTS chromophore through the reaction between ABTS and potassium persulfate. This chromophore has three absorption maxima at wavelengths of 645, 734, and 815 nm. The addition of antioxidants to this previously obtained radical follows an electron transfer mechanism **Figure 2.7**, which is visualized as a discoloration

corresponding to when the radical ABTS is reduced by antioxidant. In this way, the degree of discoloration makes it possible to evaluate the percentage of inhibition of the ABTS cation radical, which is determined as a function of the antioxidant concentration and the reaction time. [120]

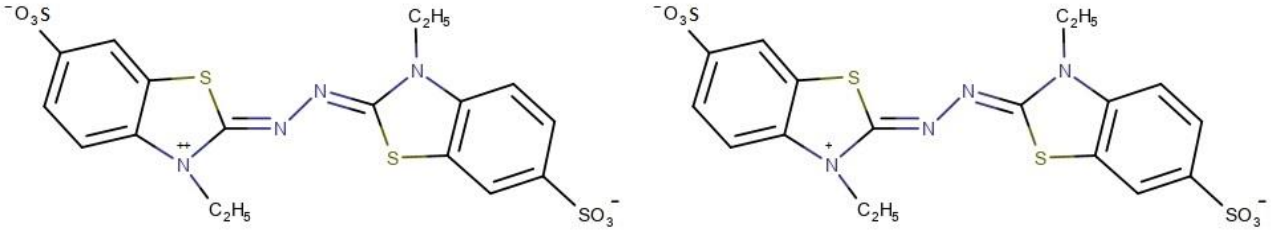


Figure 2.7 ABTS Chemical Reaction with Antioxidant Compound.

3. Computational Theories

3.1 Molecular Mechanics Methods

Methods of molecular mechanics (MM) are commonly utilized to give molecules relatively precise structures and energies. The approach incorporates basic concepts of vibrational spectroscopy as well as the belief that bonds have natural lengths and angles, also, that geometries that can better fulfill these natural values should be adopted. These methods calculations use the approximation 'Born-Oppenheimer 'which describes the molecule's energy in terms of the nuclear positions. It is the so-called surface of energy potentials. Calculations of molecular mechanics then employ an empirically constructed set of equations for the 'Born-Oppenheimer' surface, whose mathematical form is constructed from classical mechanics. [121] Moreover, they also assume that the atoms are the 'elementary' constituents of a molecular system as a matter of necessity to allow simulation of sufficiently large systems. [122] Some of the measurement methods in MM involve types of atoms to determine the functions and parameters that form the field of power. One single element, like a carbon atom can be characterized by different types of MM atoms, whose selection depends on different features, such as hybridization and chemical environment. The MM results had to be treated with care, as they sometimes predicted ring conformations different to those supported by experimental data. [123] MM are involved in most if not all Computational Structure-Based Drug Discovery projects. [124]

MM assumes the relative positions of the nuclei of the structurally forming atoms are a result of attractive and repulsive forces working. Different forms of bond stretching, angle bending, torsional strength, and other unbonded properties are measured using classical physics

equations, giving specific interactions and energies often known as force field. [125] This includes customizable parameters which are designed to achieve the best fit of molecules' experimental properties, such as geometries, conformational energies, structure heats or other properties. It is assumed that the respective parameters and constants of force are transferable from one molecule to another. The general field of molecular force mechanics is based on the *Westheimer* method and includes interaction functions for bond stretching, angle bending, torsion, and van der Waals, where each part can be represented by its own potential function such as:

$$V = V\,stretch + V\,bend + V\,torsion + V\,vdw$$

$$Bond\,stretch = V, = \tfrac{1}{2}\,kr(r - r0)\text{^}2$$

$$Angle\,bend = V0 = \tfrac{1}{2}\,k0(0 - 0o)\text{^}2$$

$$Torsion\,energy = V\,tor = kw(1 - \cos\ 3\,w)$$

$$Nonbonded\,or\,VDW\,interactions = V\,vdw = E\left[\left(\frac{ro}{r}\right)^{12} - 2\left(\frac{ro}{r}\right)^{6}\right] [121]$$

MM force fields include MM2, MM3, MMFF, Amber, Dreiding, and UFF, all of which are implemented in different software packages. [125] The most popular programs for small molecules are based on Allingers MM2 and MM3 force fields. [121]

3.2 Molecular Docking

Since the early 1980s, molecular docking (MD) has become such a structure-based drug design method that simulates the molecular interaction of a macromolecular partner with the strongest fitting binding mode of a ligand. It focuses on designing a number of potential conformations / orientations, namely the positions, of the ligand inside the protein binding site. [126] The docking process can be achieved by two interconnected steps: first by sampling ligand conformations in the protein's active site; then by rating those conformations through a scoring feature. Ideally, the experimental binding mode should be replicated by sampling algorithms, and the scoring function should also rank it highest among all generated conformations. [127] **Figure 2.8** illustrates the original lock-and-key proposal "Pattern," referring to the rigid docking of receptors and ligands to find the right "key" orientation to open the lock. The actual docking process, however, is so versatile that receptors and ligands need to adjust their conformation to fit well into each other. [128]

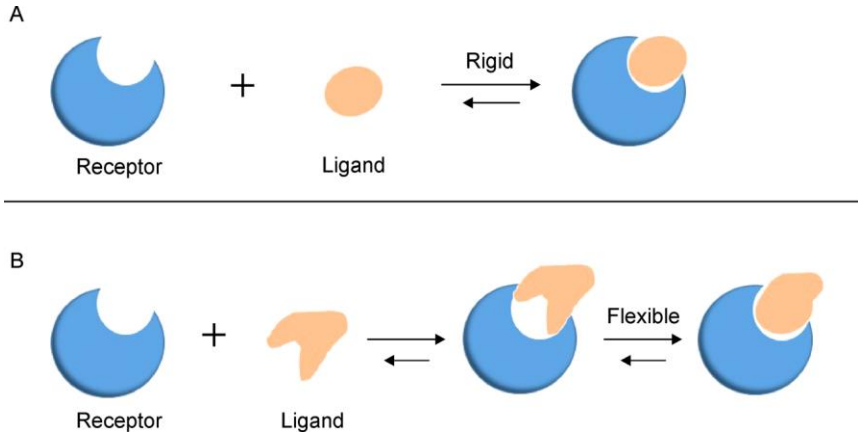


Figure 2.8 Two Models of Molecular Docking.

(A) A lock-and-key model. (B) Induced fit model.

To carry out molecular docking studies, programs based on various algorithms have been developed which have made docking an extremely important tool in pharmaceutical research. [127] **Figure 2.9** summarizes the three principal forms of molecular docking software. Flexible-rigid docking was popularly used. Because flexible docking is typically more accurate however, in recent years the related work has become the hot study spot. [128]

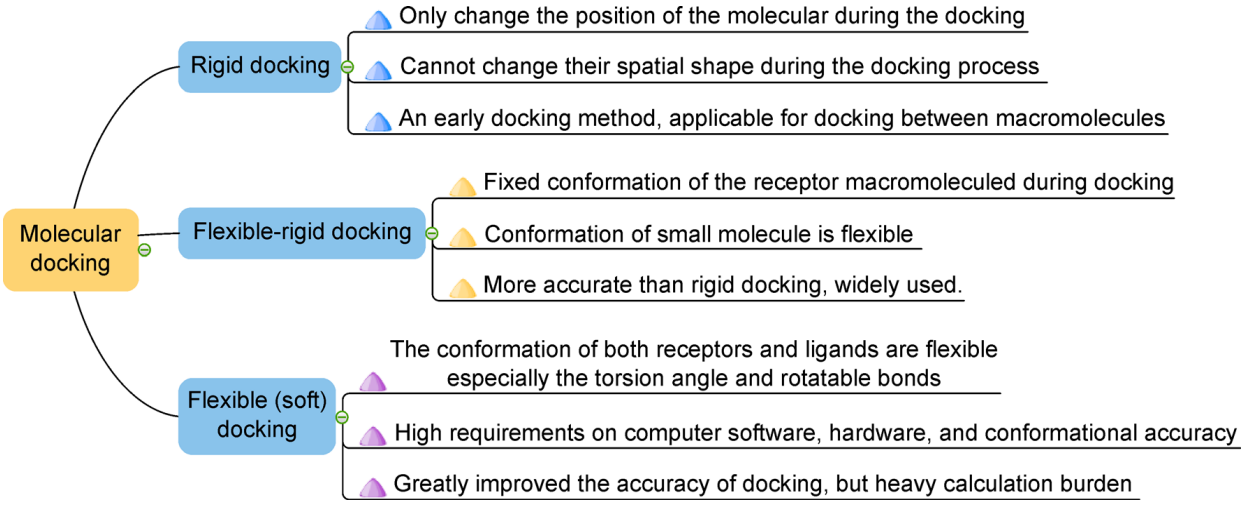


Figure 2.9 Molecular Docking Software Classification.

3.3 Density Functional Theory

Density functional theory (DFT) is one of the most widely used methods for ab initio calculations of the structure of atoms, molecules, crystals, surfaces, and their interactions. [129]

DFT provides a first-principle method for the quantum-mechanical synopsis of electrons and bypasses the need for a multi-electron wavefunction to be calculated directly. DFT-based approximations include approximations of local-spin-density (LSD) and approximations of gradients. These approximations are used widely and effectively to forecast, understand and modeling physical and chemical processes related to molecules and materials. [130] DFT calculations based on pseudopotentials, a plane-wave base set, and a supercell geometry are now considered traditional for conducting first-principle studies of semiconductor defects, while DFT in local density approximation (LDA) offers a description of the multi-body electronic ground state in terms of single-particle equations and an effective potential. The effective potential consists of the ionic potential due to the atomic cores, the Hartree potential representing the electrostatic electron interaction and the potential for exchange-correlation that takes into account the effects of several bodies. This approach has been proven to describe quantities such as formation energies, atomic geometries, charging densities, etc., with high precision. [131]

4. Quantitative Structure-Activity Relationship (QSAR)

Nowadays, one cannot talk about drug design and discovery without mentioning quantitative structure-activity relationship (QSAR) analysis, this latter was founded by Corwin Hansch in the early 1960s. The field of QSAR modeling has been in constant advancement ever since [132] and has grown tremendously with respect to the diversity of both methodologies and applications. More than 50 years of continuous improvements, interdisciplinary breakthroughs, and community-driven developments were needed to make QSAR one of the commonly employed approaches to model the physical and biological properties of chemicals in use today. In fact, QSAR modeling is widely practiced in academy, industry, and government institutions around the world. [133] As well as having broad application for assessing potential impacts of chemicals, materials, and nanomaterials on human health and ecological systems. Moreover, it is employed in numerous fields from drug design to environmental toxicology. [134]

QSAR, in simplest terms, is a method for building computational or mathematical models [135] that applies statistical analysis of relationships between chemical structure and biological activity in a quantitative and mechanism-oriented manner.[136] QSAR analysis seeks to relate the changes in the observed property to numerical descriptors, with the goal of predicting novel compounds with the desired properties.[137] QSAR has been applied for decades in the

development of relationships between physicochemical properties of chemical substances and their biological activities to obtain a reliable statistical model for prediction of the activities of new chemical entities. As with any scientific discipline QSAR throughout its entire history, has drawn both praise and criticism concerning its reliability, limitations, successes, and failures. Nevertheless, one cannot deny that QSAR is a useful alternative to conventional synthesis methods due to them being expensive and time-consuming, not only that, but also, biological assays are too costly, often requiring time, a sacrifice of animals, or compounds in their pure forms. Hence why it has now been globally apprehended by the contemporary drug discovery community that QSAR, based on well-established principles of statistics, is intrinsically a valuable and viable medicinal chemistry tool that will continue to impact the in silico drug discovery research. [134]

Like other data mining techniques, QSAR is carried out in successive steps including data set preparation, descriptor calculation, descriptor selection, model building, and validation. The success of a QSAR study relies deeply on how each of these steps is performed. [138] There are many ways in which erroneous or misleading models can be produced. For instance, there can be issues with the data or the inappropriate use of the statistical method. While there are rarely issues with the descriptors themselves, except when they are themselves based on models. A QSAR model is founded on a few ingredients. The first of these is a set of chemical structures that are represented by molecular descriptors. Molecular descriptors are typically sets of numbers that represent aspects of the chemical structure and that allow the application of mathematical functions, such as distance calculations. In addition to the molecular descriptors, a set of observed ‘activities’ must be associated with the structures. These activities can be any form of experimental observation and are not limited to biological activities. Given a set of chemical structures, each of which is represented by descriptors and with associated activities. A statistical modeling method is used to identify the key relationships between the molecular descriptors and the activities. These relationships constitute the QSAR model and can be used to predict the activities of new compounds directly from their chemical structures. Many different statistical methods can be used to generate QSAR models. [137] Among other things, QSAR methods are categorized into classes **Table 2.18**, based on the structural representation or the way by which the descriptor values are derived. [135]

Table 2.18 QSAR Classes

1D	Correlating activity with global molecular properties like pKa, log P, etc.
2D	Correlating activity with structural patterns like connectivity indices, 2D - pharmacophores, etc., without taking into account the 3D-representation of these properties
3D	Correlating activity with non-covalent interaction fields surrounding the molecules
4D	Additionally including an ensemble of ligand configurations in 3D-QSAR
5D	Explicitly representing different induced-fit models in 4D-QSAR
6D	Further incorporating different solvation models in 5D-QSAR

Most of all, the multiple activities of polyphenols especially flavonoids as well as their structural diversity make this class of compounds a rich source for modeling lead compounds with targeted pharmacological properties. Also, the activity of flavonoids is closely linked to their structure differentiation of flavonoids, but it is not easy, because thousands of them share a common phenyl-benzo-pyrone skeleton and they differ from one to another only in the position and number of hydroxyl and/or methoxyl groups, as well as the position and number of different saccharides involved in glycosylation. These diverse substitution patterns make the flavonoids an ideal object of QSAR studies. [139]

5. Software

Throughout our research, multiple software were used. First, MarvinSketch was used for the 2D drawing of the various polyphenols structures [140]. Second, Minitab was used for the statistical analysis of our data. [141]. Autodock the molecular modeling simulation software was also employed. Third, we applied both programming languages; R and Python (especially the RDKit package).

5.1 AVOGADRO

Avogadro is a molecular modeling program that provides us with 3D models of our molecules. We used it to conduct a pre-optimization for our molecules both natural and radicals

using the Steepest Descent algorithm with a convergence of 10 e^{-6} and the MMFF94s force field, this latter is particularly good with organic compounds and has specifically been parameterized for phenols and other organic compounds as well. MMFF94 and MMFF94s use the same functional form to calculate the potential energy. They only differ in the Torsion and Out-Of-Plane bending parameters used. The 's' in MMFF94s stands for static hence, it's more suited for tasks where the output is static. [142] Afterward, Avogadro was employed to perform a conformational analysis.

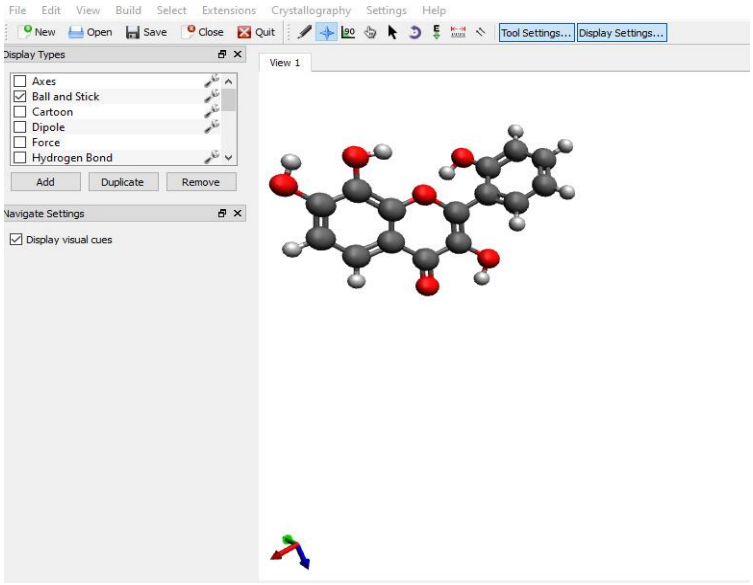


Figure 2.10 Graphical Interface of AVOGADRO Software

5.2 MOPAC

The MOPAC (Molecular Orbital PACkage) calculation was operated on input files using both the PM6 and PM7 methods. The input files are composed of each molecule's atomic coordinates and also of the keywords we chose based on what we wished to be calculated and printed. As a result, we extracted the values of the heat of formation, the dipole moment, the total energy, and lastly the values of HOMO and LUMO of each molecule.

5.3 Jmol

Jmol is an open-source viewer of molecular structures, it was used to provide us a visualization of our natural molecules as well as the HOMO, LUMO shapes, and electrostatic potential surfaces (EPS).

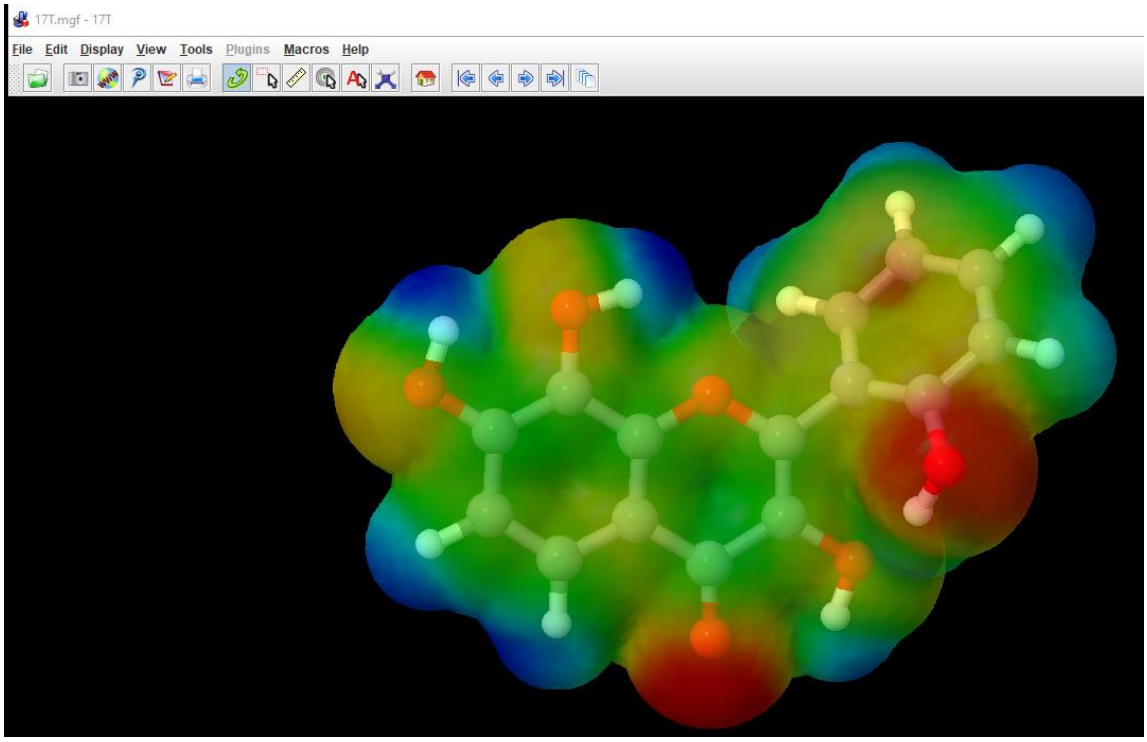


Figure 2.11 Graphical Interface of Jmol Software

6. Computers:

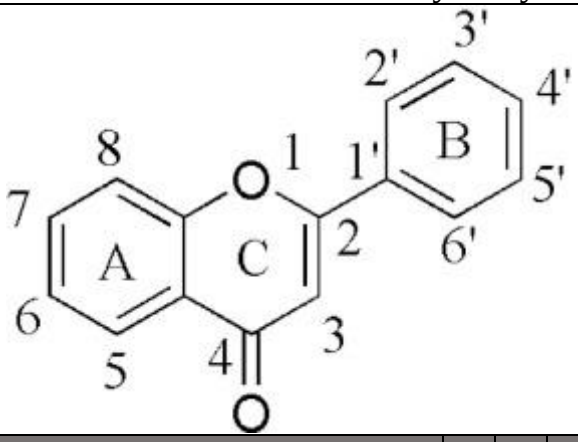
This study was done on a computer with the following characteristics:
- A laptop with an i3-5005U 2.00GHz processor running on Windows 10 pro with 4 GB RAM and a 64-bit operating system.

III. Chapter Results and Discussions

1. Molecules Set

The molecule set selected for this study is composed of 50 flavonoids. Their nomenclatures and structures are shown in **Table 3.19.**

Table 3.19 Nomenclature and Structures of Hydroxyflavone Derivatives



NUMBER	NOMENCLATURE	R3	R5	R6	R7	R8	R2'	R3'	R4'	R5'
1	3,2'-Dihydroxyflavone	OH	H	H	H	H	OH	H	H	H
2	3,5-Dihydroxyflavone	OH	OH	H	H	H	H	H	H	H
3	3',5'-Dihydroxyflavone	H	H	H	H	H	H	OH	H	OH
4	3,5,7-Trihydroxyflavone (galangin)	OH	OH	H	OH	H	H	H	H	H
5	5,7,8-Trihydroxyflavone	H	OH	H	OH	OH	H	H	H	H
6	7,8,2'-Trihydroxyflavone	H	H	H	OH	OH	OH	H	H	H
7	6,2',3'-Trihydroxyflavone	H	H	OH	H	H	OH	OH	H	H
8	6,3',4'-Trihydroxyflavone	H	H	OH	H	H	H	OH	OH	H
9	7,3',4'-Trihydroxyflavone	H	H	H	OH	H	H	OH	OH	H
10	3,7,3',4'-Tetrahydroxyflavone (fisetin)	OH	H	H	OH	H	H	OH	OH	H
11	3,6,2',3'-Tetrahydroxyflavone	OH	H	OH	H	H	OH	OH	H	H
12	3,6,3',4'-Tetrahydroxyflavone	OH	H	OH	H	H	H	OH	OH	H
13	3,6,2',4'-Tetrahydroxyflavone	OH	H	OH	H	H	OH	H	OH	H
14	7,3',4',5'-Tetrahydroxyflavone	H	H	H	OH	H	H	OH	OH	OH
15	5,6,7,4'-Tetrahydroxyflavone(6-hydroxyapigenin)	H	OH	OH	OH	H	H	H	OH	H
16	7,8,3',4'-Tetrahydroxyflavone	H	H	H	OH	OH	H	OH	OH	H
17	3,7,8,2'-Tetrahydroxyflavone	OH	H	H	OH	OH	OH	H	H	H
18	6,7,3',4'-Tetrahydroxyflavone	H	H	OH	OH	H	H	OH	OH	H

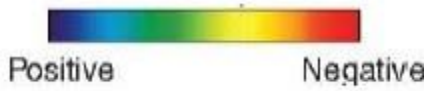
19	3,5,7,2',4'-Pentahydroxyflavone (morin)	OH	OH	H	OH	H	OH	H	OH	H
20	3,5,7,3',4'-Pentahydroxyflavone(quercetin dehydrate)	OH	OH	H	OH	H	H	OH	OH	H
21	5,7,3',4',5'-Pentahydroxyflavone	H	OH	H	OH	H	H	OH	OH	OH
22	3,6,2',4',5'-Pentahydroxyflavone	OH	H	OH	H	H	OH	H	OH	OH
23	3,7,3',4',5'-Pentahydroxyflavone	OH	H	H	OH	H	H	OH	OH	OH
24	3,5,7,8,3',4'-Hexahydroxyflavone (gossypetin)	OH	OH	H	OH	OH	H	OH	OH	H
25	3,3',4'-Trihydroxyflavone	OH	H	H	H	H	H	OH	OH	H
26	7,8,3'-Trihydroxyflavone	H	H	H	OH	OH	H	OH	H	H
27	3,6,2'-Trihydroxyflavone	OH	H	OH	H	H	OH	H	H	H
28	3,5,7,2'-Tetrahydroxyflavone (datiscetin)	OH	OH	H	OH	H	OH	H	H	H
29	3,5,7,4'-Tetrahydroxyflavone (kaempferol)	OH	OH	H	OH	H	H	H	OH	H
30	3,5,7,3',4',5'-Hexahydroxyflavone (myricetin)	OH	OH	H	OH	H	H	OH	OH	OH
31	Flavone		H	H	H	H	H	H	H	
32	6-Hydroxyflavone		H	OH	H	H	H	H	H	
33	2'-Hydroxyflavone		H	H	H	H	OH	H	H	
34	3'-Hydroxyflavone		H	H	H	H	H	OH	H	
35	4'-Hydroxyflavone		H	H	H	H	H	H	OH	
36	5,3'-Dihydroxyflavone		OH	H	H	H	H	OH	H	
37	7,2'-Dihydroxyflavone		H	H	OH	H	OH	H	H	
38	7,3'-Dihydroxyflavone		H	H	OH	H	H	OH	H	
39	7,4'-Dihydroxyflavone		H	H	OH	H	H	H	OH	
40	2',3'-Dihydroxyflavone		H	H	H	H	OH	OH	H	
41	2',4'-Dihydroxyflavone		H	H	H	H	OH	H	OH	
42	5,7,2'-Trihydroxyflavone		OH	H	OH	H	OH	H	H	
43	5,3',4'-Trihydroxyflavone		OH	H	H	H	H	OH	OH	
44	6,7,3'-Trihydroxyflavone		H	OH	OH	H	H	OH	H	
45	7,8,4'-Trihydroxyflavone		H	H	OH	OH	H	H	OH	
46	5,7,3',4'-Tetrahydroxyflavone (Luteolin)		OH	H	OH	H	H	OH	OH	
47	5-Hydroxyflavone(Primuletin)		OH	H	H	H	H	H	H	
48	5,7-Dihydroxyflavone(Chrysin)		OH	H	OH	H	H	H	H	
49	5,4'-Dihydroxyflavone		OH	H	H	H	H	H	OH	
50	3',4'-Dihydroxyflavone		H	H	H	H	H	OH	OH	

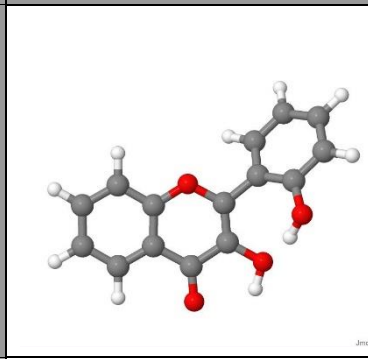
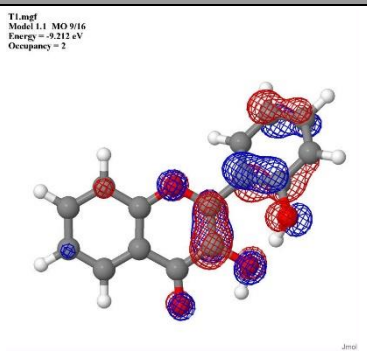
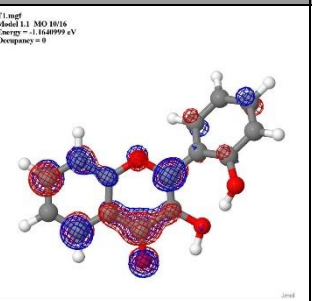
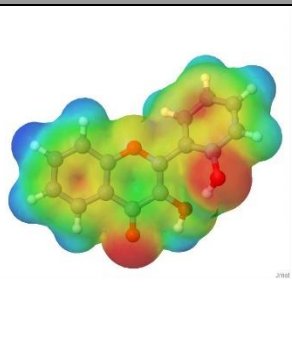
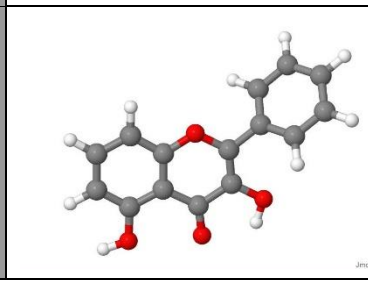
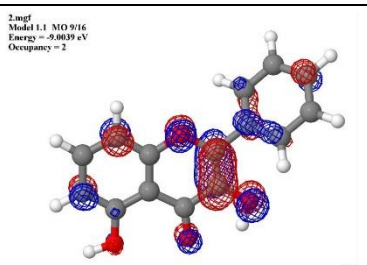
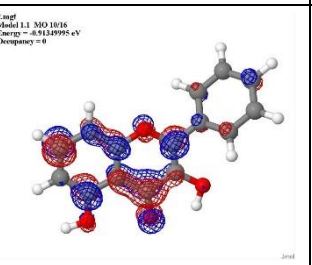
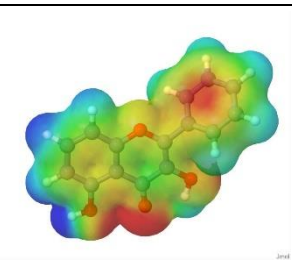
2. HOMO, LUMO, and MEPS

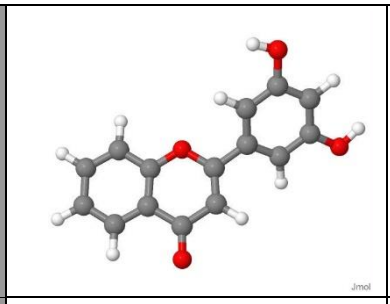
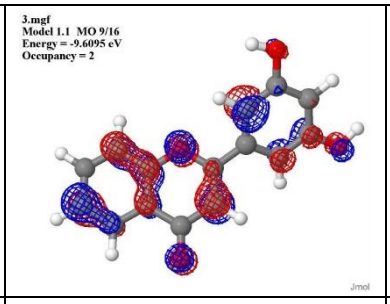
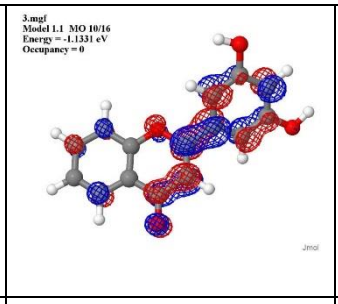
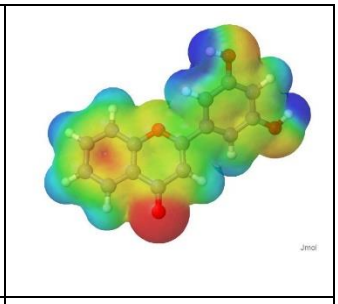
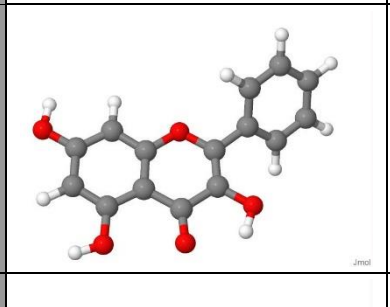
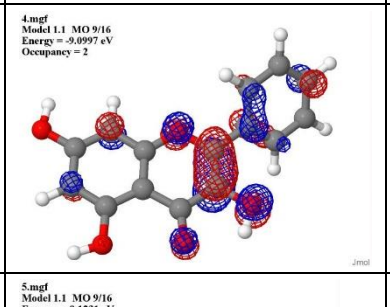
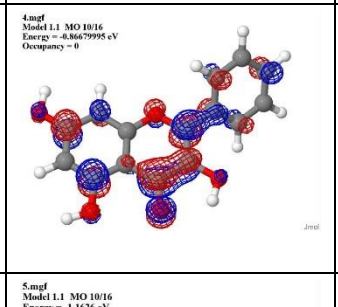
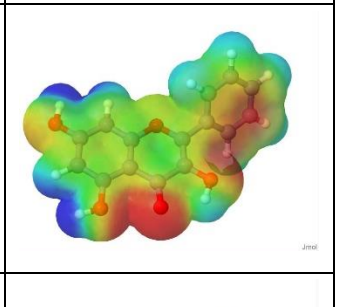
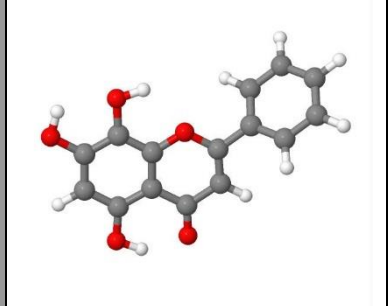
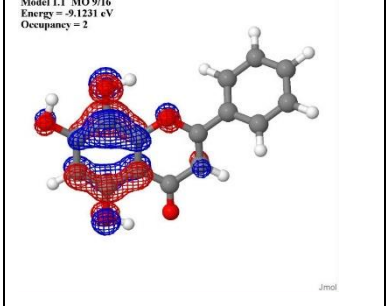
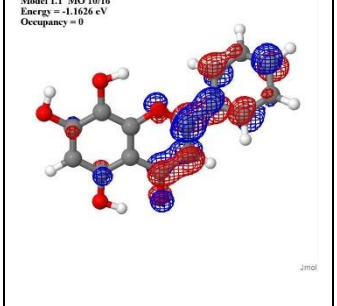
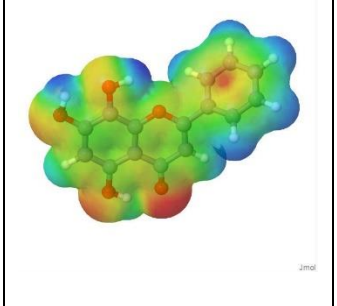
Molecular Electrostatic Potential Surface (MEPS) map illustrates the charge distributions of a molecule three-dimensionally. This map is used to visualize variably charged regions of a molecule. The HOMO and LUMO as well as the MEPS of each molecule **Table 3.20** (the rest are summarized in the annex)

As shown in **Table 3.20**, the electrostatic potential surfaces are represented by different colors i.e., red for most electronegative potential regions, blue for most positive electrostatic potential and green for regions of zero potential (as shown on the head of **Table 3.20**). MEPSs are mostly similar and show that the high electronic density (suitable for electrophilic attack) is located on the oxo, hydroxy functions.

Table 3.20 HOMO, LUMO, and Molecular Electrostatic Potential Surface MEPS



Number	Molecule	HOMO	LUMO	Electrostatic Potential
1				
2				

3				
4				
5				

3. Bond Dissociation Enthalpies (BDEs) and Quantum-Molecular Descriptors

We generated several Semi-empirical Quantum-Molecular Descriptors as shown in **Table 3.21** (PM6) and **Table 3.22** (PM7): SUM of BDE, LUMO, HOMO, DM (Dipole Moment), in addition to the experimental DPPH scavenging effect in percentage.

Table 3.21 PM6 BDEs and Some Quantum-Chemical Molecular Descriptors/sBDE

NUMBER	SUM of BDE	1/sBDE	LUOMO	HOMO	DM	Scv (%)
1T	70.0654	0.01427237981	-1.249	-9.264	4.06951	69.3
2	65.3576	0.01530043943	-0.973	-9.026	4.02141	58.3
3	76.5874	0.01305697804	-1.18	-9.614	4.72716	61.8
4	126.1757	0.007925456328	-0.948	-9.131	4.109	52.5
5	116.0101	0.008619939126	-1.228	-9.151	6.74637	58.8
6	102.3498	0.009770414793	-1.135	-9.36	2.68672	79.9
7	100.9589	0.009905020756	-1.369	-9.311	1.81133	87.1

8	97.8263	0.01022219996	-1.187	-9.216	5.9915	83.9
9	105.0687	0.009517582306	-1.11	-9.32	3.93373	84.9
10T	140.863	0.007099096285	-1.23	-8.986	2.54665	85.2
11T	134.774	0.00741982875	-1.572	-9.108	5.20537	86.6
12T	162.9	0.006138735421	-1.439	-8.924	3.6117	86.7
13T	148.017	0.006755980732	-1.443	-9.146	4.10316	86.3
14T	131.225	0.007620499143	-1.256	-9.239	2.98545	88.8
15T	126.334	0.007915525512	-0.976	-9.35	3.9253	69.9
16	125.21	0.007986582541	-1.144	-9.22	4.52583	87.4
17T	138.649	0.007212457356	-1.397	-9.351	3.13795	83.1
18	123.886	0.008071937103	-1.24	-9.374	4.68772	86.4
19T	216.675	0.004615207107	-1.328	-9.411	3.3632	81.5
20T	190.001	0.005263130194	-1.086	-8.939	3.39571	87.8
21	180.053	0.005553920235	-1.169	-9.159	5.27083	88.1
22T	162.398	0.006157711302	-1.53	-8.872	4.25894	85.6
23T	166.065	0.006021738476	-1.345	-8.935	3.15914	79.9
24T	208.878	0.004787483603	-1.241	-9.007	1.91152	85.4
25T	97.2015	0.01028790708	-1.242	-8.937	2.88001	85.7
26T	102.3319	0.009772123844	-1.242	-9.422	3.85646	87.1
27T	106.538	0.009386322251	-1.466	-9.212	2.90641	86.8
28T	154.386	0.006477271255	-1.068	-9.231	4.85553	86.5
29T	171.015	0.005847440283	-1.206	-9.207	3.86208	77.2
30T	225.904	0.004426659112	-1.466	-9.007	2.82614	79.5
31	0	0	-0.929	-9.548	4.44287	0
32	33.2687	0.03005828301	-1.068	-9.131	5.78287	7.9
33	37.6279	0.02657602471	-1.053	-9.561	3.33437	3.8
34	35.5033	0.0281663958	-1.088	-9.566	3.79348	5.9
35	36.9125	0.0270910938	-0.901	-9.484	5.1961	4.2
36T	84.5515	0.01182711129	-1.231	-9.409	6.24486	2
37	78.7069	0.01270536637	-1.086	-9.612	4.2217	3.1
38T	40.7205	0.02455765524	-1.114	-9.607	6.40963	5.5
39	77.6229	0.01288279619	-0.94	-9.573	6.05956	4
40	65.6577	0.01523050609	-1.239	-9.285	3.02785	87.8
41	81.7863	0.01222698667	-1.015	-9.578	4.03894	40.4
42	137.7899	0.00725742598	-1.228	-9.731	5.24188	9.7
43	114.3364	0.008746121095	-1.235	-9.414	4.7784	81
44T	93.8802	0.01065187334	-1.212	-9.46	5.47726	87.8

45	102.883	0.009719778778	-1.056	-9.367	5.62905	87.7
46	154.019	0.006492705445	-1.031	-9.275	4.82911	84.8
47	39.08174	0.02558739708	-0.835	-9.419	4.56174	0.2
48	99.181	0.0100825763	-1.119	-9.681	6.59887	5.4
49	86.6001	0.01154733078	-1.043	-9.388	5.79705	5.9
50	64.217	0.01557220051	-1.084	-9.316	4.75081	84

Table 3.22 PM7 BDEs and Some Quantum-Chemical Molecular Descriptors

NUMBER	SUM of BDE	1/BDE	LUOMO	HOMO	DM	Scv (%)
1T	71.8669	0.01391461159	-1.164	-9.212	3.58865	69.3
2	63.9019	0.01564898696	-0.913	-9.004	3.65085	58.3
3	76.9231	0.0129999961	-1.133	-9.609	4.43586	61.8
4	121.2816	0.008245273809	-0.867	-9.1	3.73326	52.5
5	118.3035	0.008452835292	-1.163	-9.123	6.42592	58.8
6	110.5401	0.009046490821	-1.064	-9.335	265673	79.9
7	106.9091	0.009353740701	-1.261	-9.354	1.59907	87.1
8	101.5333	0.009848985505	-1.124	-9.228	5.68254	83.9
9	107.2402	0.009324861386	-1.053	-9.343	3.71458	84.9
10T	141.492	0.007067537387	-1.133	-8.994	2.22937	85.2
11T	141.731	0.007055619448	-1.424	-9.148	4.68512	86.6
12T	167.381	0.005974393748	-1.321	-8.935	3.24039	86.7
13T	148.878	0.006716909147	-1.333	-9.114	3.59678	86.3
14T	135.499	0.007380128267	-1.155	-9.26	2.7714	88.8
15T	133.065	0.007515124187	-0.926	-9.29	3.48256	69.9
16	131.239	0.007619686221	-1.076	-9.222	4.45793	87.4
17T	-1247.191	-0.000801801809	-1.25	-9.304	2.80893	83.1
18	129.363	0.007730185602	-1.155	-9.383	4.48973	86.4
19T	214.338	0.004665528278	-1.228	-9.325	2.92947	81.5
20T	189.04	0.005289885738	-0.98	-8.949	3.061	87.8
21	182.03	0.005493599956	-1.071	-9.196	4.95477	88.1
22T	1119.336	0.0008933867936	-1.399	-8.864	3.88147	85.6
23T	169.695	0.005892925543	-1.217	-8.952	2.76803	79.9
24T	212.453	0.004706923414	-1.104	-8.992	1.74171	85.4
25T	99.141	0.01008664427	-1.157	-8.941	2.536	85.7
26T	105.1052	0.009514277124	-1.154	-9.43	3.67458	87.1
27T	107.2493	0.00932407018	-1.334	-9.179	2.4586	86.8
28T	152.595	0.006553294669	-0.976	-9.193	4.56043	86.5

29T	168.603	0.005931092567	-1.119	-9.181	3.57418	77.2
30T	229.367	0.004359825084	-1.314	-9.034	2.57743	79.5
31	0	0	-0.923	-9.496	4.0409	0
32	34.0751	0.02934694249	-1.028	-9.154	5.32785	7.9
33	39.381	0.02539295599	-1.019	-9.522	2.96685	3.8
34	36.4115	0.02746385071	-1.047	-9.542	3.48278	5.9
35	37.3252	0.02679155102	-0.9	-9.434	4.78985	4.2
36T	86.4181	0.01157164992	-1.185	-9.388	5.92018	2
37	79.4394	0.01258821189	-1.042	-9.58	3.84451	3.1
38T	39.9824	0.02501100484	-1.076	-9.588	6.08048	5.5
39	77.3043	0.01293589102	-0.925	-9.513	5.66259	4
40	71.0875	0.01406717074	-1.15	-9.315	2.80547	87.8
41	82.115	0.01217804299	-0.993	-9.486	3.67067	40.4
42	136.6245	0.007319331452	-1.172	-9.675	4.83754	9.7
43	117.984	0.008475725522	-1.163	-9.394	4.55598	81
44T	97.6035	0.01024553423	-1.155	-9.412	5.086	87.8
45	105.85	0.009447170478	-1	-9.385	5.35104	87.7
46	153.65	0.00650829808	-0.966	-9.3	4.59275	84.8
47	39.31861	0.02543324904	-0.826	-9.370	4.11387	0.2
48	96.583	0.01035378897	-1.086	-9.591	6.18368	5.4
49	87.8451	0.01138367422	-1.028	-9.366	5.40054	5.9
50	67.2234	0.01487577242	-1.030	-9.322	4.46636	84

4. QSAR Models

The following QSAR models were generated to describe the antioxidant activity of 50 flavonoids, based on 4 Semi empirical Quantum -Molecular Descriptors **Table 3.21** and **Table 3.22**. Using multiple linear regression (MLR) analysis techniques, a genetic algorithm and the live one out cross validation as implemented in MINITAB software.

4.1 PM6 Model

QSAR Equation:

AA = - 2244,4561 (± 1244,0346) 1/sBDE - 76,4748 (± 49,9235) HOMO - 5,1090 (± 66,3380)

(A)

(n = 50; R = 0,677) As given by the model's equation (A), n is the number of compounds is the correlation coefficient

Table 3.23 Correlation Matrix PM6

Correlation matrix	1/sBDE	HOMO
1/sBDE	1	0
HOMO	0	1

Figure 3.10 shows a plot of the observed versus calculated AA, and **Figure 3.11** shows a plot of the observed versus residual antioxidant activity.

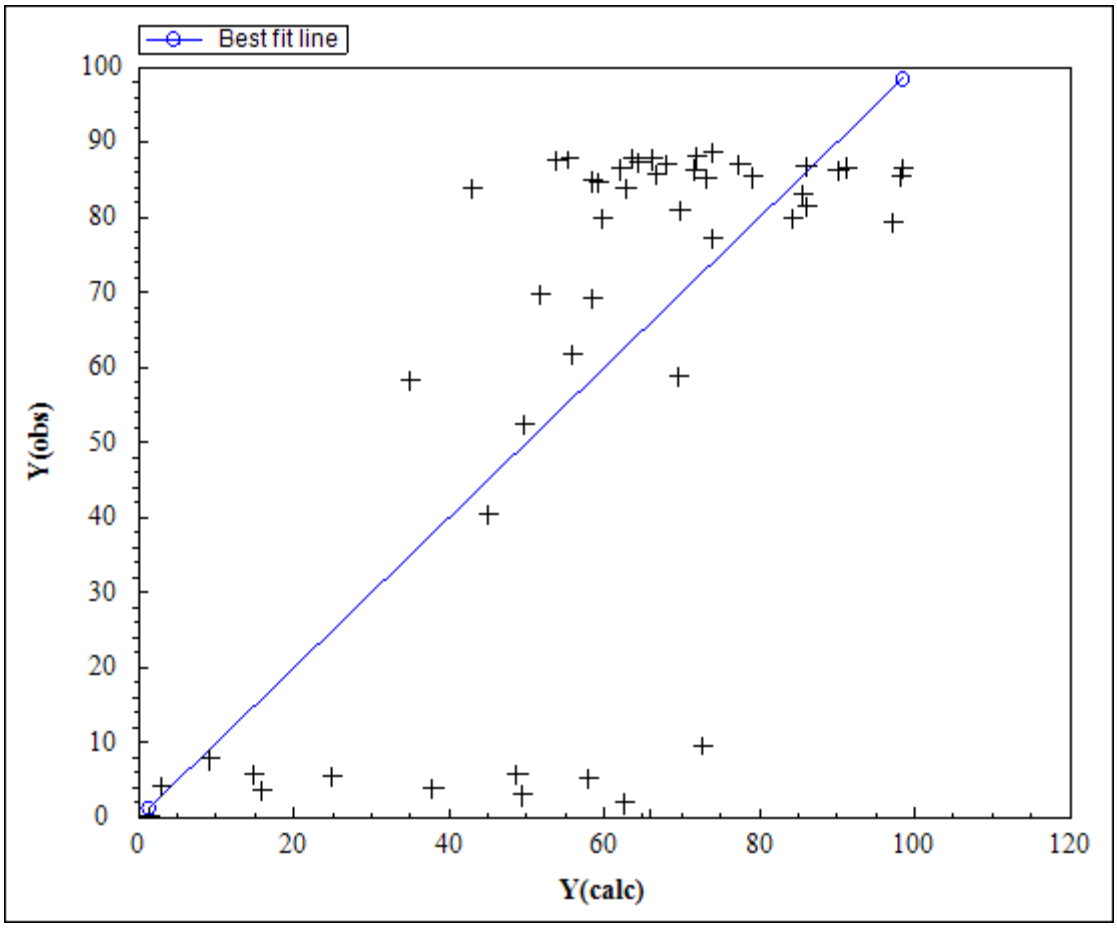


Figure 3.10 Plot of PM6 observed versus calculated AA for QSAR model described by EqXX

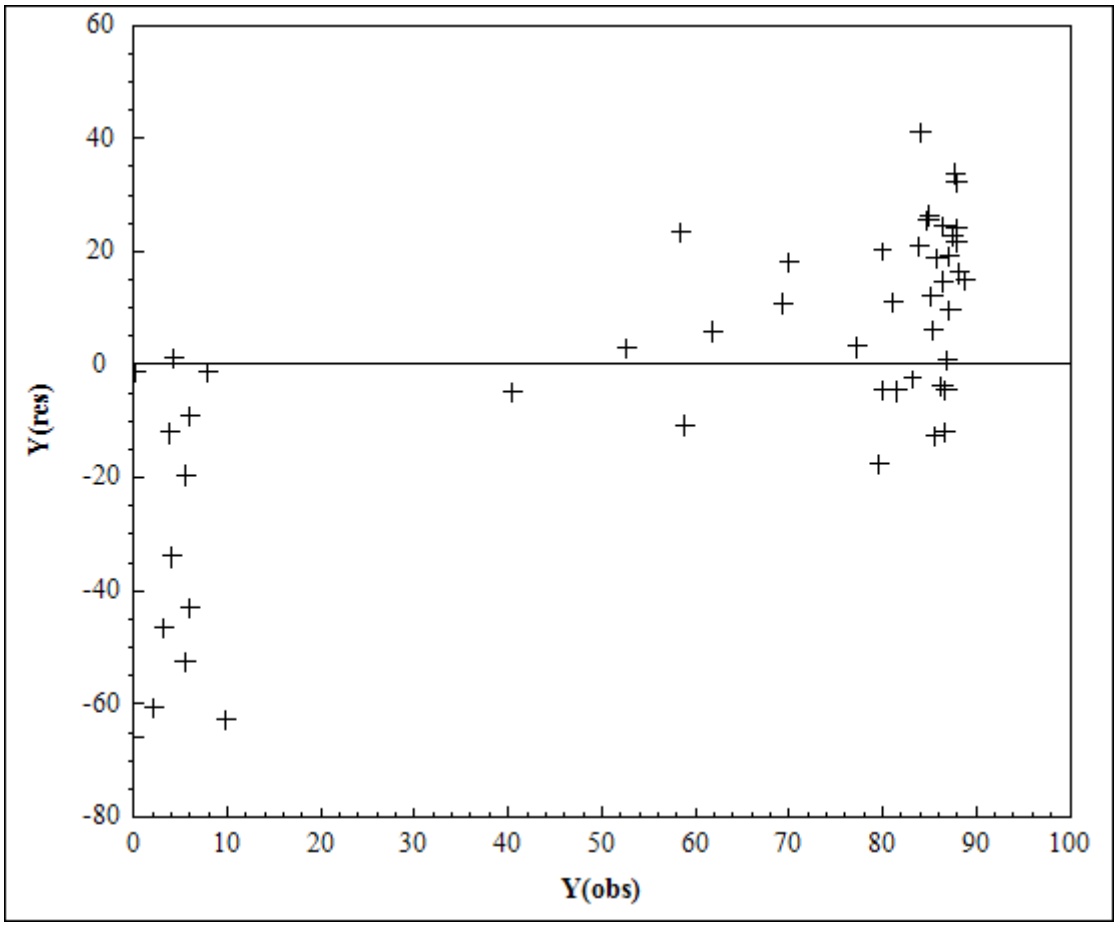


Figure 3.11 Plot of PM6 observed versus residual AA for QSAR model described by Eq XX

4.2 PM7 Model

QSAR Equation

AA = - 0,0408 (± 0,0340) BDE - 3174,8714 (± 1310,4119) 1/sBDE - 38,0216 (± 53,1953) HOMO + 62,4704 (± 36,1344) LUMO - 9,8099 (± 5,8691) pLog(1/sBDE) + 658,8515 (± 346,8407)

(B)

(n = 50; R = 0,796) As given by the model's equation (B), n is the number of compounds is the correlation coefficient.

Table 3.24 Correlation Matrix PM7

	BDE	1/sBDE	HOMO	LUMO	pLog(1/sBDE)
BDE	1	69	0,145	0,290	523
1/sBDE	69	1	0,419	0,382	458
HOMO	145	419	1	0,318	52
LUMO	290	382	0,318	1	32
pLog(1/sBDE)	523	458	0,052	0,032	1

Figure 3.12 shows a plot of the observed versus calculated AA, and **Figure 3.13** shows a plot of the observed versus residual antioxidant activity.

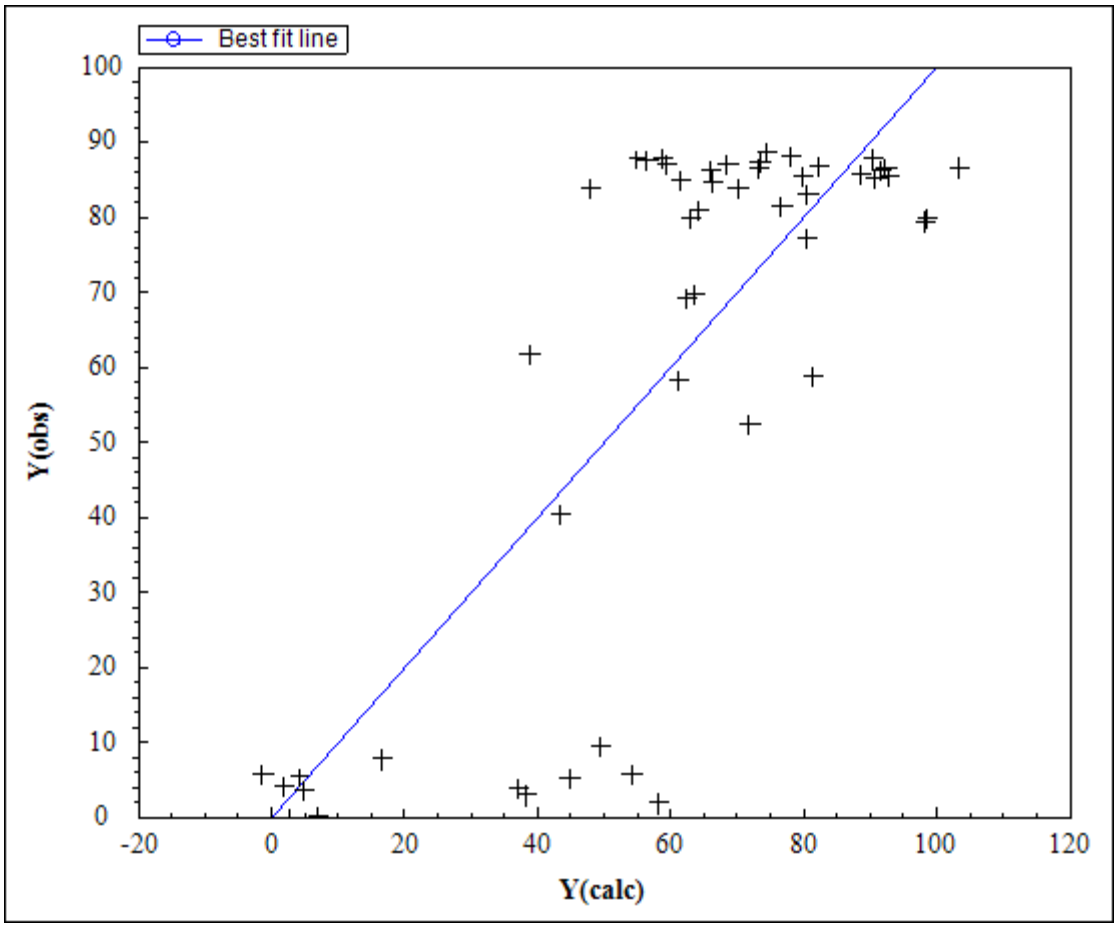


Figure 3.12 Plot of PM7 observed versus calculated AA for QSAR model described by EqXX.

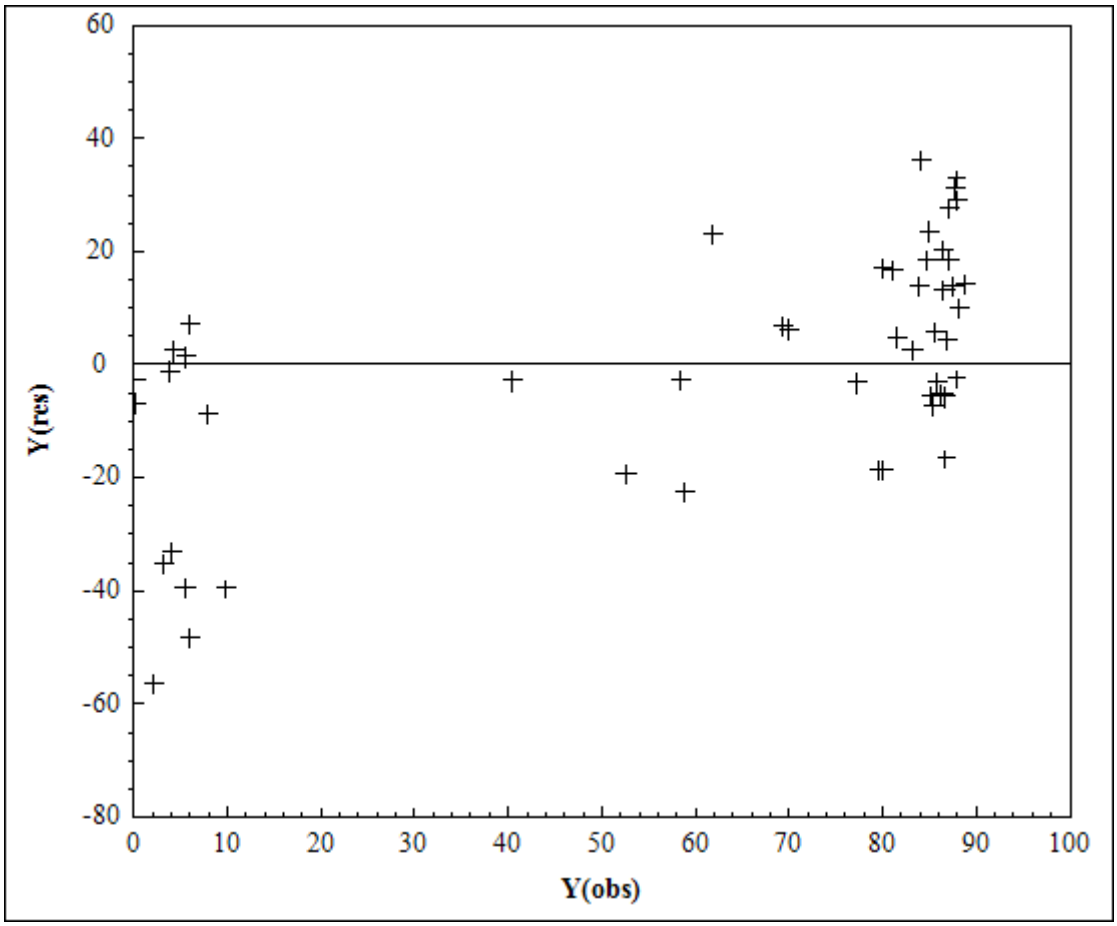
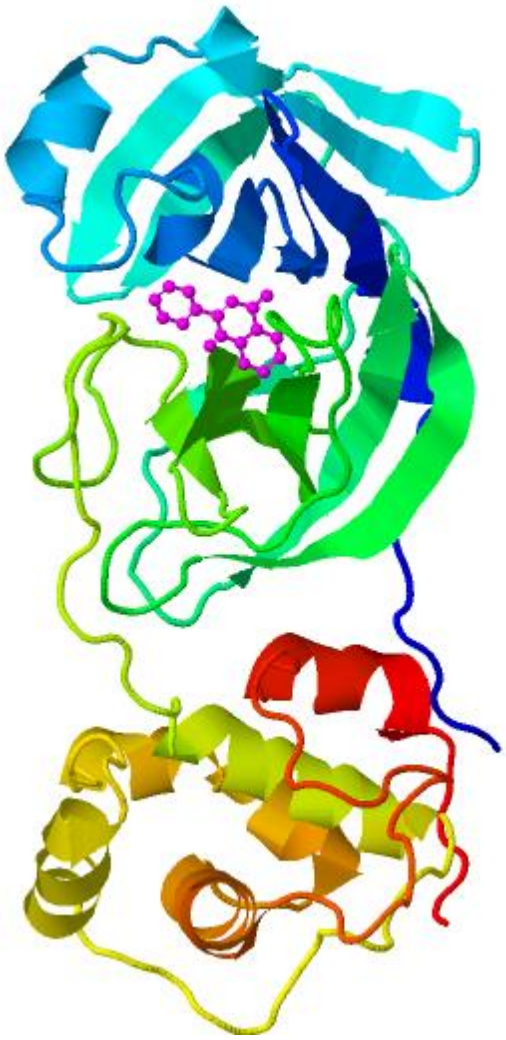


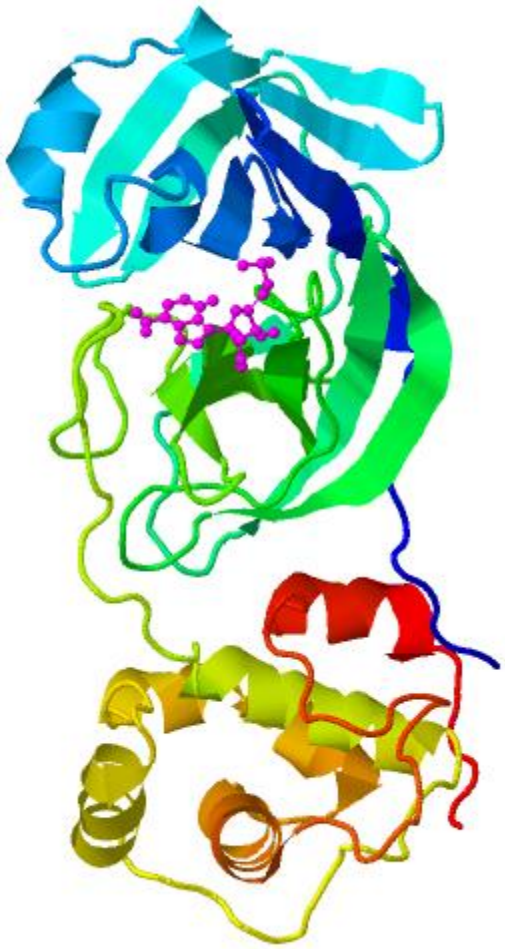
Figure 3.13 Plot of PM7 observed versus residual AA for QSAR model described by Eq XX.

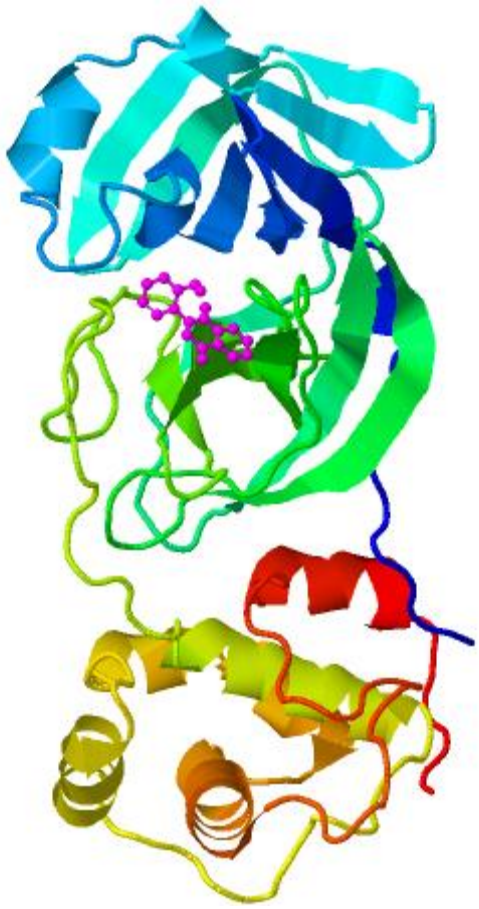
5. Docking in SARS-COV2

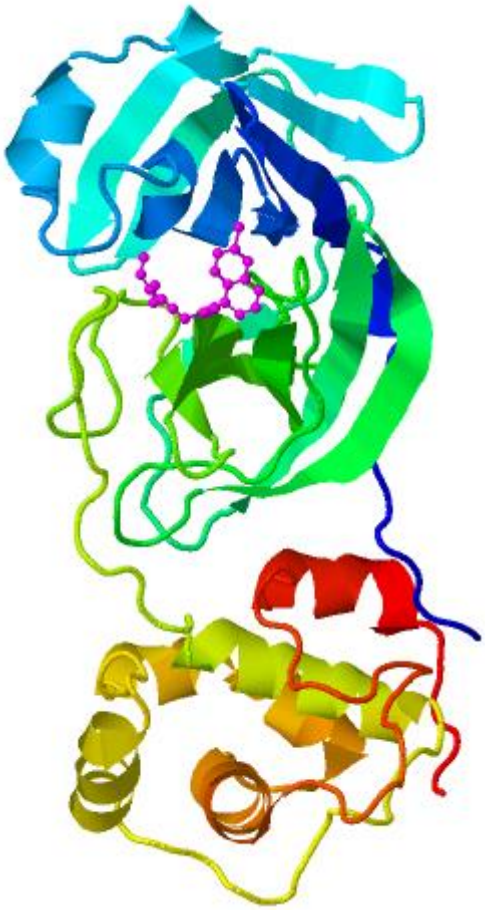
AUTODOCK Vina was used to evaluate the inhibition potential of Flavone, 2'-Hydroxyflavone, Remdesivir and Chloroquine (the two latter as references) against SARS-COV2 as shown in **Table 3.25**. As a result, the SARS-COV2 inhibition potential trend was as follows: Flavone (-7 kcal/mol) > Remdesivir (-7 kcal/mol) > 2'-Hydroxyflavone (-6.8 kcal/mol) > Chloroquine (-6.3 kcal/mol).

Table 3.25 Docking SARS-COV2 Results

Compound	Score (kcal/mol)	Docking Picture
Flavone	**-7**	

Remdesivir	**-7**	

2'-Hydroxyflavone	**-6.8**	

Chloroquine	**-6.3**	

Conclusion

This study was performed on Polyphenols compounds, -more precisely on 50 Flavonoids, to examine their antioxidant priorities. Which refers to their ability to prevent harmful damages caused by Reactive Oxygen Species (ROS). Many studies have shown the antioxidant power of flavonoids and flavonoid-rich extracts and their ability to augment oxidative defense hence preventing tumor generation. This preventive property -known as the radical scavenging- is processed by various chemical mechanisms: Hydrogen Atom Transfer (HAT), Singlet Electron Transfer (SET), and Sequential Proton Loss Electron Transfer (SPLET). In this study we adopted the HAT mechanism and its associated Bond Dissociation Enthalpies (BDEs). This study was performed to generate robust Quantitative Structure-Activity Relationship (QSAR) models which could predict in Silico, the antioxidant activity of hypothetical or newly designed flavonoids.

Based on QSAR Modelling: On one hand, the PM7 semiempirical method could explain the antioxidant activity in function of 5 Quantum-Molecular Descriptors: BDE, 1/BDE, HOMO, LUMO, and pLog(1/BDE) with a correlation coefficient R= 0,796. On the other hand, the PM6 semiempirical could explain the antioxidant activity in function of only 2 descriptors: 1/sBDE and HOMO but with a correlation coefficient R= 0,677. These models gave good predictions regarding their residuals and correlation coefficients.

Flavone, 2'-Hydroxyflavone, Remdesivir and Chloroquine were docked in SARS-COV2 protein and as a result the SARS-COV2-inhibition potential trend was as follows: Flavone (-7 kcal/mol)> Remdesivir (-7 kcal/mol) > 2'-Hydroxyflavone (-6.8 kcal/mol) > Chloroquine (-6.3 kcal/mol).

As a perspective, these QSAR models could be used in addition to an (in construction) algorithm to predict new potent (antioxidant) flavonoid-based structures not yet discovered or unproduced by nature.

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Annexes

Table 1.2 Polyphenol and Antioxidant Content in the 100 Richest Foods (mg per 100 g or mg per 100 ml)

Food	Food group	Polyphenols		Polyphenols AE		Antioxidants	
		Content	Rank	Content	Rank	Content	Rank
Cloves	Seasonings	15 188	1	15 188	1	16 047	1
Peppermint dried	Seasonings	11 960	2	7920	2	980	2
Star anise	Seasonings	5 460	3	5 460	3	1 810	16
Cocoa powder	Cocoa products	3 448	4	3 294	4	1 104	24
Mexican oregano dried	Seasonings	2 319	5	2 137	5	—	—
Celery seed	Seasonings	2 094	6	1 007	10	—	—
Black chokeberry	Fruits	1 756	7	1 432	7	1 752	17
Dark chocolate	Cocoa products	1 664	8	1 618	6	1 860	13
Flaxseed meal	Seeds	1 528c	9	1220c	8	—	—
Black elderberry	Fruits	1359	10	804	13	1950	12
Chestnut	Seeds	1215	11	1215	9	2757	9
Common sage dried	Seasonings	1207	12	893	12	2920	8
Rosemary,dried	Seasonings	1018	13	522	14	2519	10
Spearmint dried	Seasonings	956	14	491	18	6575	3
Common thyme dried	Seasonings	878	15	464	19	1815	15

Lowbush blueberry	Fruits	836	16	496	15	471	35
Blackcurrant	Fruits	758	17	464	20	821	29
Capers	Seasonings	654	18	389	21	3600	6
Black olive	Vegetables	569	19	320	22	117	53
Highbush blueberry	Fruits	560	20	295	23	205	40
Hazelnut	Seeds	495	21	493	16	687	30
Pecan nut	Seeds	493	22	493	17	1816	14
Soy flour	Seeds	466	23	267	27	—	—
Plum	Fruits	377	24	285	24	411	35
Green olive	Vegetables	346	25	233	28	161	47
Sweet basil, dried	Seasonings	322	26	166	34	4317	4
Curry powder	Seasonings	285	27	285	25	1075	25
Sweet cherry	Fruits	274	28	145	38	144	48
Globe artichoke heads	Vegetables	260	29	154	35	1142	23
Blackberry	Fruits	260	30	180	33	570	31
Roasted soybean	Seeds	246	31	153	36	—	—
Milk chocolate	Cocoa products	236	32	236	27	854	28
Strawberry	Fruits	235	33	205	29	268	36
Red chicory	Vegetables	235	34	131	41	129	51

Red raspberry	Fruits	215	35	107	46	980	27
Coffee, filter	Non-alcoholic beverages	214	36	110	45	267	37
Ginger dried	Seasonings	202	37	202	30	473	32
Whole grain hard wheat flour	Cereals	201c	38	201c	21	186	46
Prune	Fruits	194	39	100	49	1195	21
Almond	Seeds	187	40	185	32	191	45
Black grape	Fruits	169	41	124	42	205	41
Red onion	Vegetables	168	42	99	50	91	60
Green chicory	Vegetables	166	43	117	44	—	—
Common thyme fresh	Seasonings	163	44	118	43	1173	23
Refined maize flour	Cereals	153c	45	153c	37	102	59
Soy tempeh	Seeds	148	46	101	48	—	—
Whole grain rye flour	Cereals	143c	47	143c	39	72	66
Apple	Fruits	136	48	136	40	205	42
Spinach	Vegetables	119	49	68	55	248	38
Shallot	Vegetables	113	50	67	56	115	54
Lemon verbena, dried	Seasonings	106	51	106	47	—	—
Black tea	Non-alcoholic beverages	102	52	90	52	104	58

Red wine	Alcoholic beverages	101	53	91	51	215	39
Green tea	Non-alcoholic beverages	89	54	82	53	62	67
Soy yogurt	Seeds	84	55	51	60	—	—
Yellow onion	Vegetables	74	56	49	61	75	64
Soy meat	Seeds	73	57	47	63	—	—
Whole grain wheat flour	Cereals	71c	58	71c	54	90	61
Pure apple juice	Non-alcoholic beverages	68	59	61	57	34	75
Pure pomegranate juice	Non-alcoholic beverages	66	60	37	64	204	43
Extra-virgin olive oil	Oils	62	61	33	67	55	70
Black bean	Seeds	59	62	36	66	1390	20
Peach	Fruits	59	63	54	59	107	57
Pure blood orange juice	Non-alcoholic beverages	56	64	28	71	72	67
Cumin	Seasonings	55	65	55	58	2038	11
Pure grape, fruit juice	Non-alcoholic beverages	53	66	23	76	54	72
White bean	Seeds	51	67	31	69	138	49
Chinese cinnamon	Seasonings	48	68	48	62	—	—

Pure blond, orange juice	Non-alcoholic beverages	46	69	20	81	—	—
Broccoli	Vegetables	45	70	21	79	198	44
Redcurrant	Fruits	43	71	23	77	448	36
Soy tofu	Seeds	42	72	25	74	—	—
Pure lemon juice	Non-alcoholic beverages	42	73	20	82	—	—
Whole grain oat flour	Cereals	37c	74	37c	65	82	65
Apricot	Fruits	34	75	15	85	133	53
Caraway	Seasonings	33	76	33	68	2913	7
Refined rye flour	Cereals	31c	77	31c	70	45	74
Asparagus	Vegetables	29	78	11	90	75	65
Walnut	Seeds	28	79	28	71	1576	19
Potato	Vegetables	28	80	15	86	54	73
Ceylan cinnamon	Seasonings	27	81	27	73	9070	2
Parsley dried	Seasonings	25	82	25	75	1584	18
Nectarine	Fruits	25	83	20	83	55	71
Curly endive	Vegetables	24	84	15	87	—	—
Marjoram dried	Seasonings	23	85	22	78	3,846	5
Red lettuce	Vegetables	23	86	14	88	114	58

Chocolate beverage with milk	Non-alcoholic beverages	21	87	21	80	—	—
Quince	Fruits	19	88	12	89	—	—
Endive (Escarole)	Vegetables	18	89	11	91	—	—
Soy milk	Non-alcoholic beverages	18	90	11	92	—	—
Pure pomelo juice	Non-alcoholic beverages	18	91	7.9	97	—	—
Rapeseed oil	Oils	17	92	17	84	18	78
Pear	Fruits	17	93	11	93	108	59
Soybean sprout	Seeds	15	94	10	95	—	—
Green grape	Fruits	15	95	7.6	98	122	55
Carrot	Vegetables	14	96	6.6	100	58	71
Vinegar	Seasonings	13	97	11	94	—	—
Soy cheese	Seeds	12	98	7.6	99	—	—
White wine	Alcoholic beverages	10	99	8.6	96	32	77
Rose wine	Alcoholic beverages	10	100	7.8	98	82	63

Table 1.3 Food Servings Providing at Least 1 mg Polyphenols with Their Polyphenol and Antioxidant Contents (mg per serving)

Food	Food group	Servinga (g)	Polyphenols		Polyphenols AE		Antioxidants	
			Content	Rank	Content	Rank	Content	Rank
Black elderberry	Fruits	145d	1 956	1	1 196	2	2 808	1
Black chokeberry	Fruits	145d	1 595	2	1 114	1	2 523	2
Blackcurrant	Fruits	145d	1 092	3	689	4	1 182	5
Highbush blueberry	Fruits	145d	806	4	425	5	321	14
Globe artichoke heads	Vegetables	168	436	5	259	8	1918	3
Coffee filter	Non-alcoholic beverages	190	408	6	209	13	507	11
Lowbush blueberry	Fruits	145d	395	7	714	3	678	8
Sweet cherry	Fruits	145d	394	8	209	14	249	20
Strawberry	Fruits	166d	390	9	340	6	480	12
Blackberry	Fruits	144d	374	10	260	9	821	6
Plum	Fruits	85	320	11	242	11	349	13
Red raspberry	Fruits	144	310	12	154	17	213	22

Flaxseed meal	Seeds	20e	306f	13	244f	10	—	—
Dark chocolate	Cocoa products	17	283	14	275	7	316	15
Chestnut	Seeds	19	230	15	231	12	524	10
Black tea	Non-alcoholic beverages	195	197	16	175	15	204	23
Green tea	Non-alcoholic beverages	195	173	17	164	16	121	31
Pure apple juice	Non-alcoholic beverages	248	168	18	151	18	84	38
Apple	Fruits	110	149	19	147	19	221	21
Whole grain rye bread	Cereals	120	146f	20	146f	20	—	—
Hazelnut	Seeds	28e	138	21	138	21	192	24
Red wine	Alcoholic beverages	125	126	22	117	23	269	19
Soy yogurt	Seeds	125	105	23	53	28	—	—
Cocoa powder	Cocoa products	3	103	24	99	25	33	46
Pure pomegranate juice	Non-alcoholic beverages	150	99	25	50	31	306	16

Soy flour	Seeds	20e	93	26	53	29	—	—
Black grape	Fruits	54	91	27	113	24	92	36
Black olive	Vegetables	15	85	28	48	32	17	56
Pure grape, fruit juice	Non-alcoholic beverages	150	79	29	39	37	82	39
Pure blood orange juice	Non-alcoholic beverages	154	71	30	31	42	111	33
Milk chocolate	Cocoa products	32	75	31	75	26	273	17
Spinach	Vegetables	59	70	32	40	34	170	26
Pecan nut	Seeds	15	69	33	69	27	272	18
Prune	Fruits	32	62	34	32	40	—	—
Redcurrant	Fruits	144	62	35	119	22	646	9
Soy, tempeh	Seeds	40	59	36	40	35	—	—
Peach	Fruits	99e	59	37	52	30	105	34
Soy tofu	Seeds	130	54	38	32	41	—	—
Green olive	Vegetables	15	52	39	35	39	24	51
Black bean	Seeds	35	52	40	14	56	1216	4

Red onion	Vegetables	30	50	41	30	43	31	47
Green grape	Fruits	54	48	42	46	33	66	41
White bean	Seeds	35	44	43	11	60	121	32
Chocolate beverage with milk	Non-alcoholic beverages	187	39	44	39	38	—	—
Roasted soybean	Seeds	15	37	45	40	36	—	—
Potato	Vegetables	128	36	46	23	45	69	40
Shallot	Vegetables	32	36	47	21	47	—	—
Soy milk	Non-alcoholic beverages	187	34	48	20	48	—	—
Red chicory	Vegetables	14	33	49	18	49	18	54
Broccoli	Vegetables	72	33	50	15	53	142	30
Soy meat	Seeds	40e	29	51	19	50	—	—
Whole grain rye flour	Cereals	20	29f	52	29f	44	14	59
Pure pomelo juice	Non-alcoholic beverages	154	27	53	12	58	—	—
Nectarine	Fruits	99	25	54	20	48	44	44

Green chicory	Vegetables	14	23	55	16	49	—	—
Pear	Fruits	138	23	56	15	54	149	29
Beer	Alcoholic beverages	574	22	57	22	46	160	27
Yellow onion	Vegetables	30	22	58	15	55	23	52
Apricot	Fruits	65	22	59	10	61	86	37
Asparagus	Vegetables	75	22	60	8.6	64	56	42
Quince	Fruits	100	19	61	12	59	—	—
Almond	Seeds	10	19	62	0.8	88	6.2	64
Whole grain wheat flour	Cereals	20	14f	63	14f	57	18	55
White wine	Alcoholic beverages	125	13	64	10	62	40	45
Rose wine	Alcoholic beverages	125	12	65	10	63	10	62
Dark beer	Alcoholic beverages	574	10	66	5.2	67	102	35
Extra virgin olive oil	Oils	16	10	67	4.8	68	8.8	63
Soybean sprout	Seeds	60	9.3	68	6.0	66	—	—

Carrot	Vegetables	54	7.6	69	3.5	69	31	48
Bilberry	Fruits	145d	7.4	70	7.4	65	756	7
Pure lemon juice	Non-alcoholic beverages	15	6.3	71	1.8	80	—	—
Red lettuce	Vegetables	24	5.4	72	3.4	70	27	50
Soy cheese	Seeds	40e	4.9	73	3.1	72	—	—
Green bean	Vegetables	60	4.8	74	3.4	71	185	25
Curly endive	Vegetables	14	3.4	75	2.0	78	—	—
Cauliflower	Vegetables	38	2.7	76	2.7	73	31	49
Peanut roasted dehulled	Seeds	40	2.6	77	2.6	74	17	57
Rapeseed oil	Oils	16	2.5	78	2.5	75	—	—
Pumpkin	Vegetables	60	2.5	79	2.0	79	52	43
Pasta	Cereals	60	2.5	80	2.5	76	—	—
Banana	Fruits	97	2.5	81	2.5	77	150	28
Endive (escarole)	Vegetables	14	2.5	82	1.5	82	—	—
Tomato	Vegetables	50	2.1	83	1.2	83	22	53

Green lettuce	Vegetables	24	1.9	84	1.1	85	16	58
White onion	Vegetables	30	1.6	85	1.0	87	13	61
Refined oat flour	Cereals	20	1.6f	86	1.6f	81	—	—
Refined wheat flour	Cereals	20	1.2f	87	1.2f	84	14	60
Pomegranate	Fruits	100	1.1	88	1.1	86	—	—
Sweet green pepper	Vegetables	20	0.9	89	0.5	89	0.4	65

Table1.4 Number of Polyphenols Described in Each Food Group

Food group	flavonoids	Phenolic acids	stilbenes	lignans	Other polyphenols
Nonalcoholic beverages	105	49	6	2	12
Alcoholic beverages	75	33	13	7	19
Fruits	112	47	7	6	1
Vegetables	92	51	0	6	12
Cereals	33	29	0	6	2
Seeds	76	16	3	18	4

Cocoa	25	13	2	0	5
Seasonings	62	29	1	0	25
Oils	11	28	2	12	22

Table1.8 Flavonols content in foods

Flavonols	Source	Content by wt or vol mg kg^{-1} fresh wt (or mg L^{-1})
	Yellow onion	350–1200
Quercetin	Curly kale	300–600
Kaempferol	Leek	30–225
Myricetin	Cherry tomato	15–200
	Broccoli	40–100
	Blueberry	30–160
	Black currant	30–70
	Apricot	25–50
	Apple	20–40
	Beans, green or white	10–50
	Black grape	15–40
	Tomato	2–15
	Black tea infusion	30–45
	Green tea infusion	20–35

	Red wine	2–30

Table 1.14 Flavanols in Fruits and Berries.

Fruit	Flavanols (mg/100 g fresh weight)
Apple	0.1–45
Apricot	0.3–11
Avocado	0.1–0.6
Banana	0.1–10.3
Black currant	1.2
Blackberry	3.3–23.8
Blueberry	1–7
Cherry	6.3–23
Custard apple	18–25
Fig	0.1–4.8
Grape	0.1–20
Kiwi	0.3–0.8
Loquat fruit	2.5–2.9
Mango	1.7
Peach	2–17
Pear	0.4–12
Persimmon	0.4–1.7
Plum	3.7–79
Pomegranate	0.8–1.2

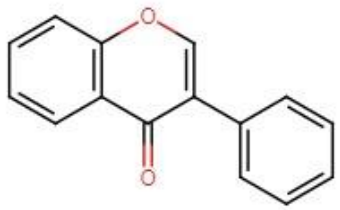
Quince	3–7
Raspberry	2–48
Red currant	2–7
Strawberry	2–6
Strawberry tree fruit	10–29

Table 1.5 The Most Studied PCs (2000–2016)

Polydatin	263
Resveratrol	7847
Pinoresinol	892
Pelargonidin	886
Delphinidin	1360
Cyanidin	2590
Neobavaisoflavone	34
Daidzein	2425
Genistein	5343
Epigallocatechin	5467
Epicatechin	5370
Catechin	9133
Eriodictyol	661

Hesperetin	1938
Naringenin	4497
Rutin	8282
Quercetin	21605
Kaempferol	7950
Galangin	1010
Apigenin	6618
Luteolin	6631
Chrysin	2126
p-Coumaric acid	723
Ferulic acid	2001
Caffeic acid	3279
Syringic acid	307
Gallic acid	4027
Vanillic acid	1372

Table 1.12 Isoflavones Basic Structure and Examples



Isoflavone	R5	R6	R7	R8	R3’	R4’	R5’
Biochanin A	OH	H	OH	H	H	OCH_3	H
Biochanin A-7-O-β-glucoside (sissotrin)	OH	H	OGlu	H	H	OCH_3	H
Calycosin	H	H	OH	H	OH	OCH_3	H
Daidzein	H	H	OH	H	H	OH	H
Daidzein-7-O-β-glucoside (daidzin)	H	H	OGlu	H	H	OH	H
Formononetin	H	H	OH	H	H	OCH_3	H
Formononetin-7-O-β-glucoside (ononin)	H	H	OGlu	H	H	OCH_3	H
Genistein	OH	H	OH	H	H	OH	H
Genistein-7-O-β-glucoside (genistin)	OH	H	OGlu	H	H	OH	H
Glycitein	H	OCH_3	OH	H	H	OH	H
Glycitein-7-O-β-glucoside (glycitin)	H	OCH_3	OGlu	H	H	OH	H
Irilone	OH	$O\text{-}CH_2\text{-}O$		H	H	OH	H
Orobol	OH	H	OH	H	OH	OH	H

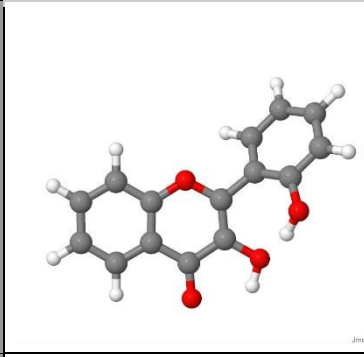
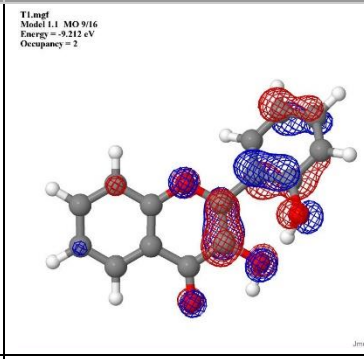
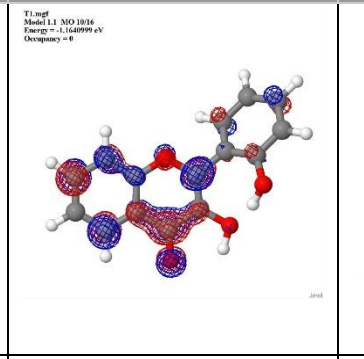
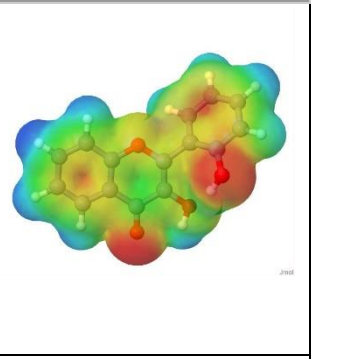
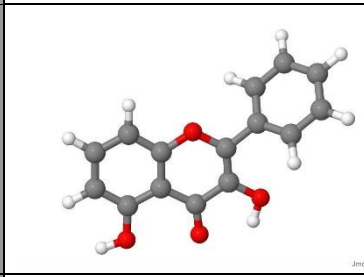
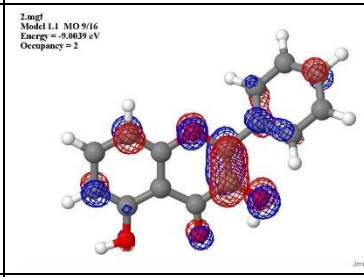
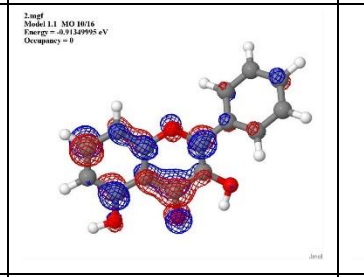
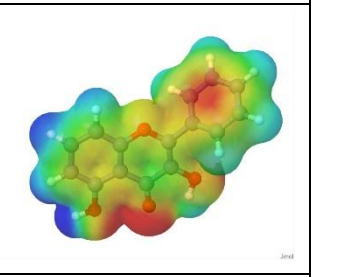
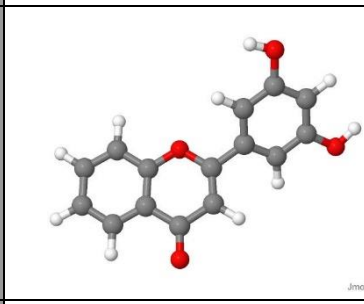
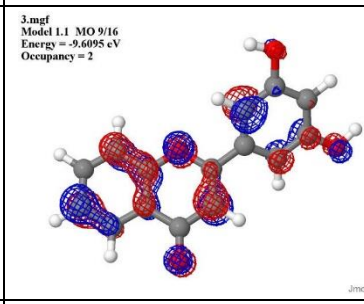
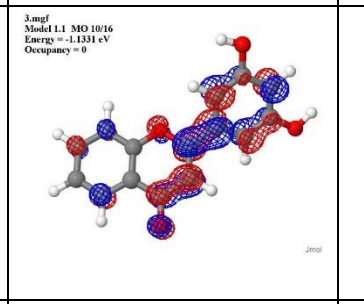
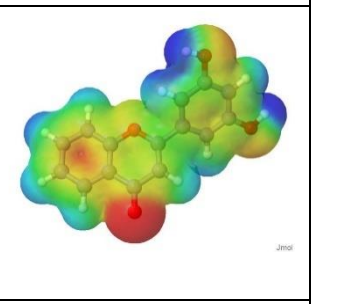
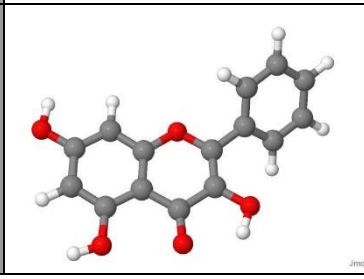
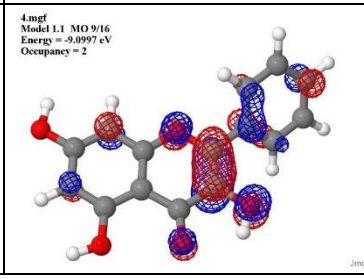
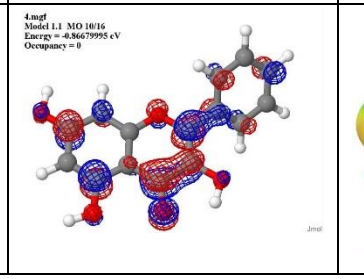
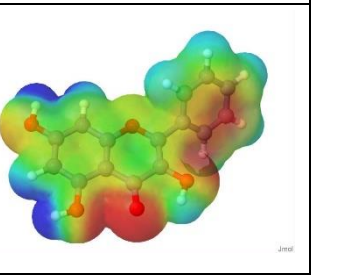
Pratensein	OH	H	OH	H	OH	OCH_3	H
Prunetin	OH	H	OCH_3	H	H	OH	H
Pseudobaptigenin	H	H	OH	H	H	$O\text{-}CH_2\text{-}O$	
Puerarin	H	H	OH	Glu	H	OH	H

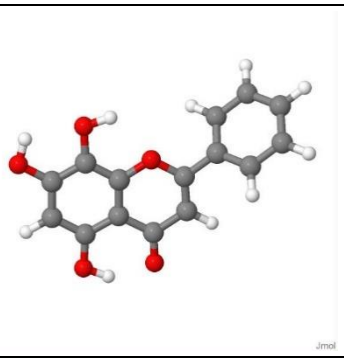
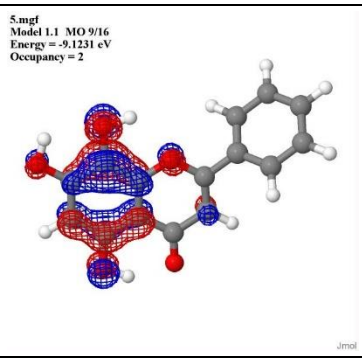
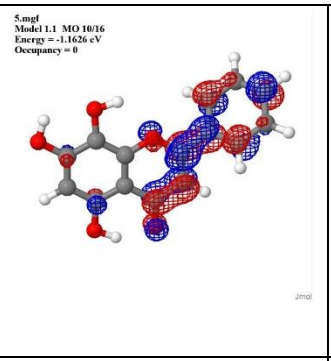
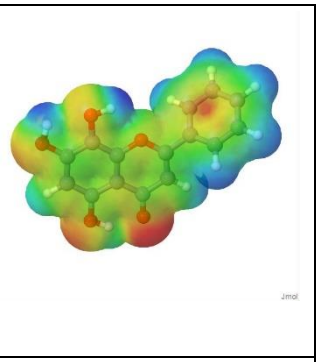
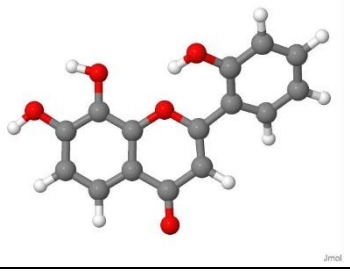
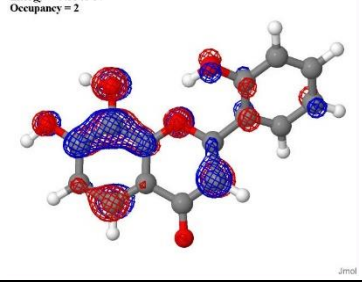
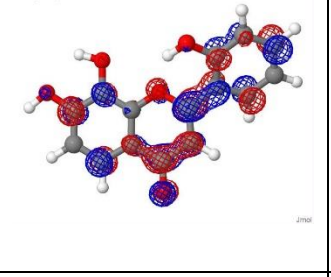
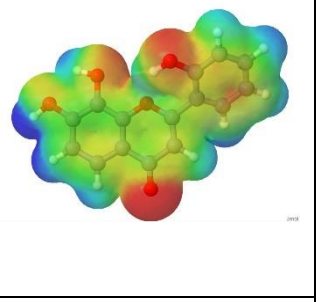
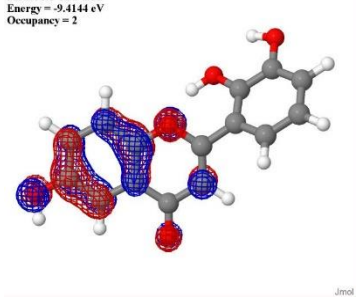
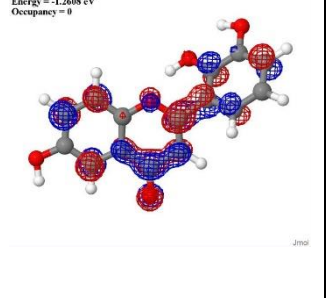
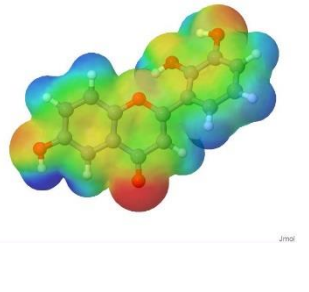
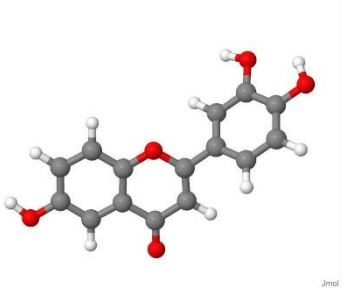
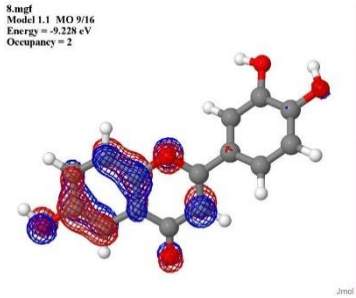
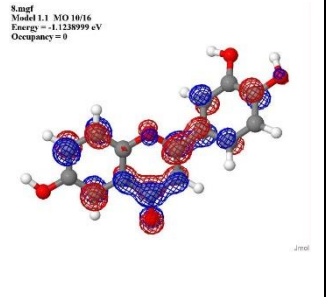
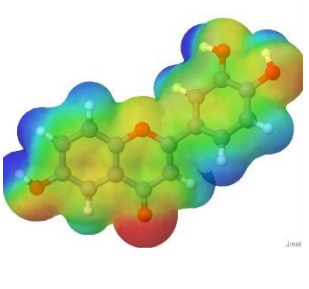
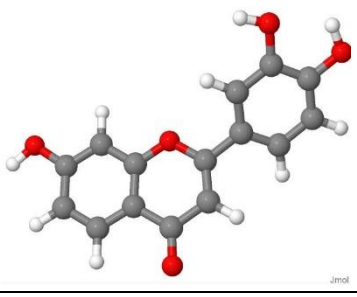
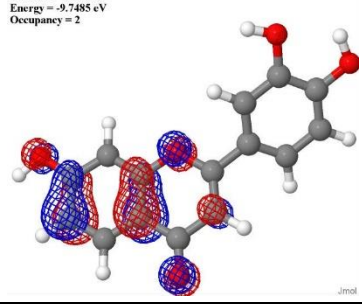
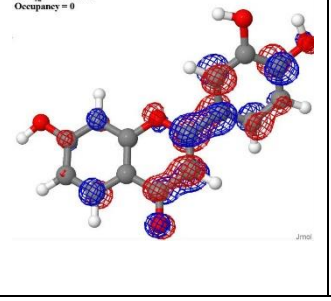
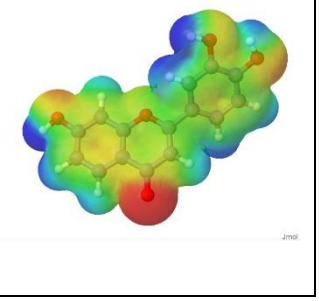
Table 1.17 Anti-inflammatory Activities of Some Phenolic Compounds

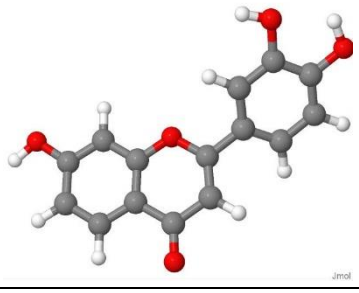
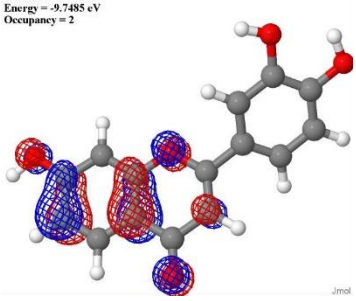
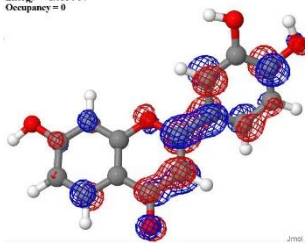
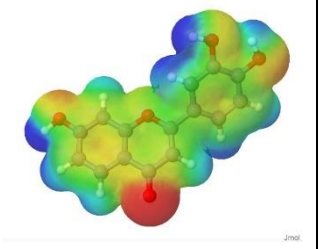
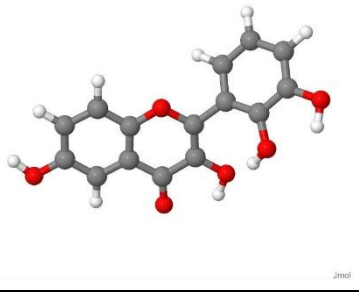
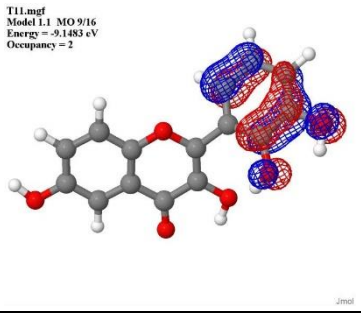
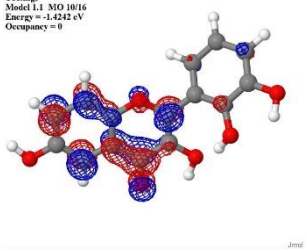
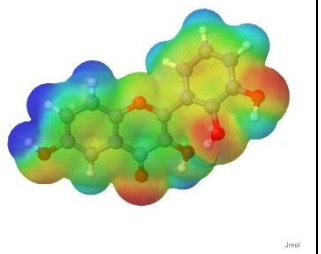
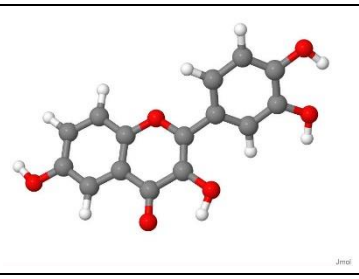
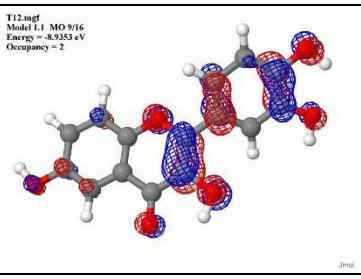
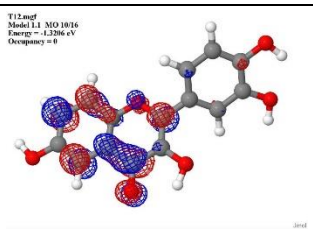
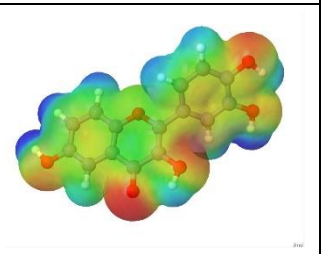
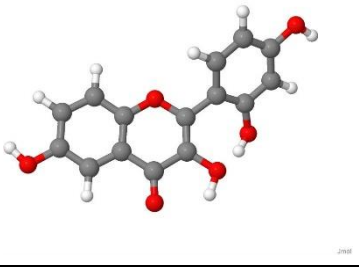
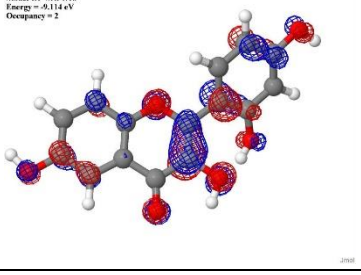
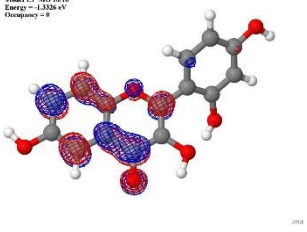
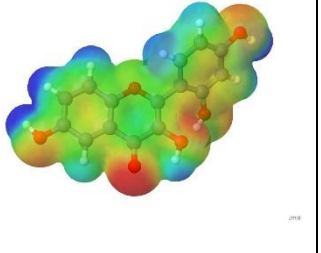
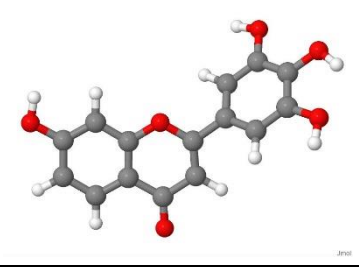
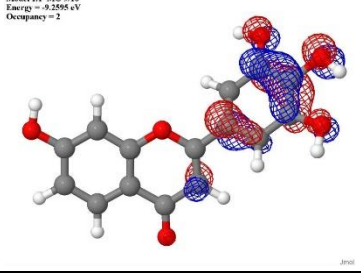
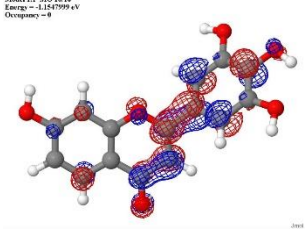
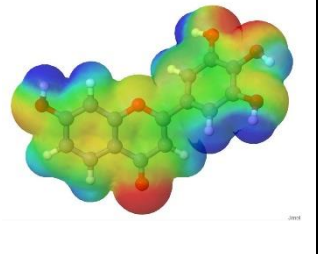
Phenolic compounds	Anti-inflammatory activities
Apegenin	Inhibiting LPS-induced inflammation
Catechin	Against monosodium urate-induced inflammation
Epigallocatechin gallate	Suppressing melanoma growth
Ellagic acid	Ameliorating monocrotaline -induced pulmonary artery hypertension
Green tea	Decreasing PCB 126 induced oxidative stress
Homoplantaginin	Inhibiting palmitic acid-induced inflammation
Luteoloside	Inhibiting proliferation, invasion, and metastasis of HCC cells
Plant polyphenols	Modulating the inflammatory response of human keratinocytes
Quercetin	Repair of kidney injury
Resveratrol	Ameliorating hepatic metaflammation
Rutin	Reducing inflammation in pancreas

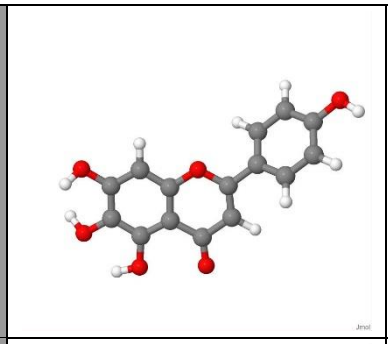
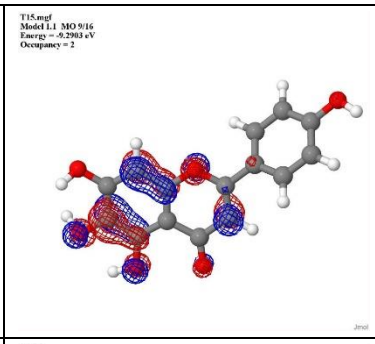
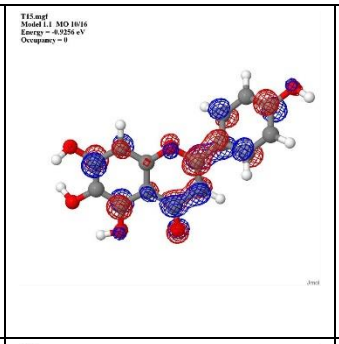
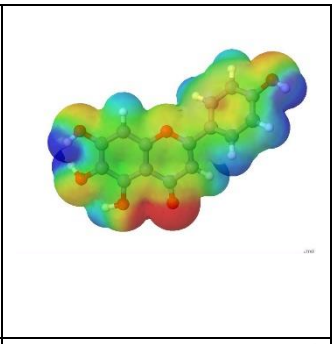
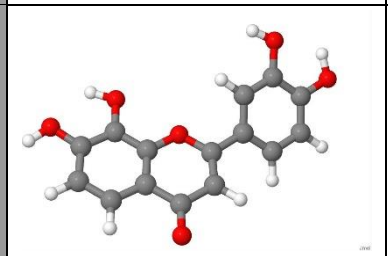
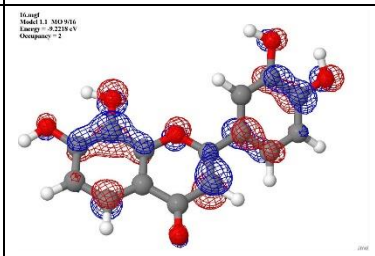
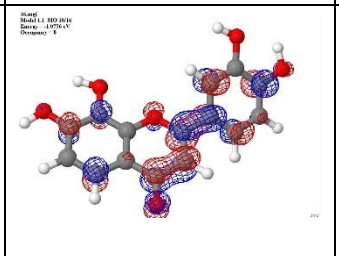
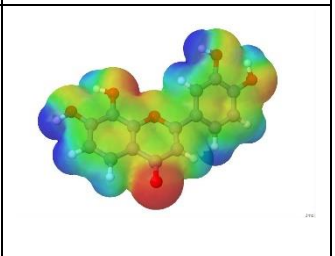
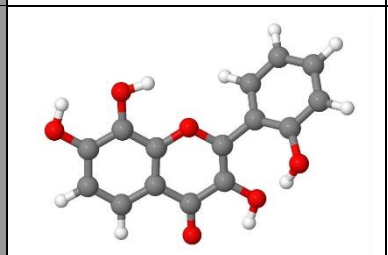
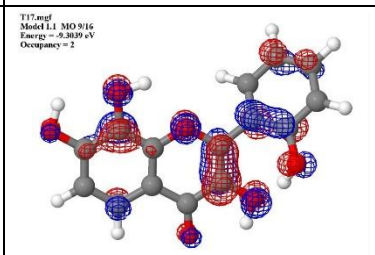
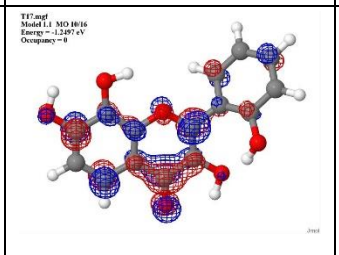
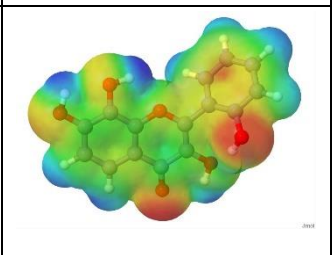
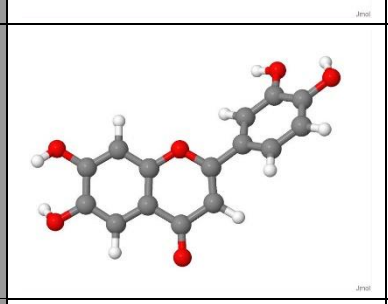
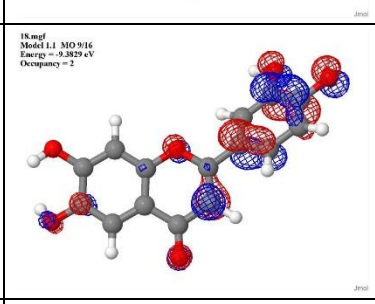
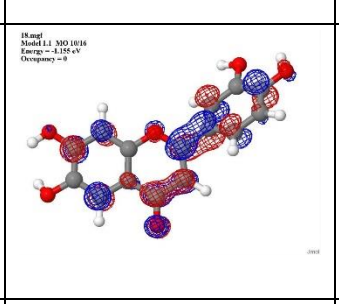
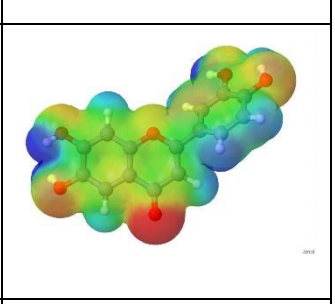
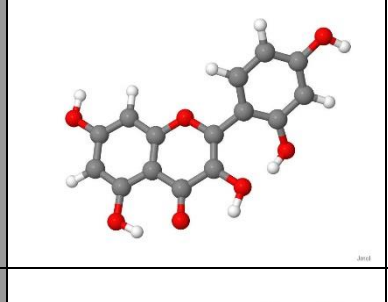
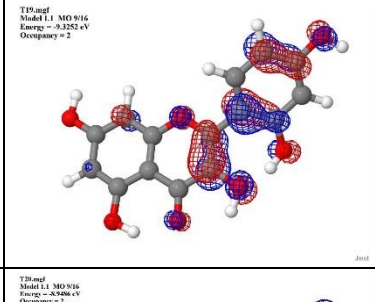
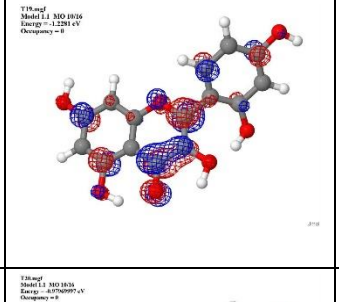
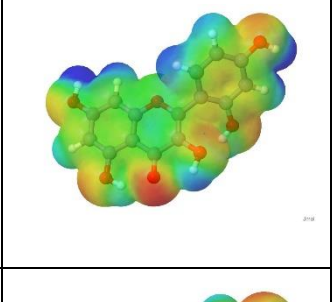
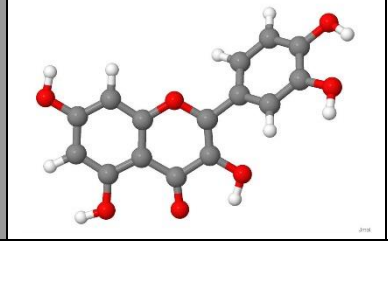
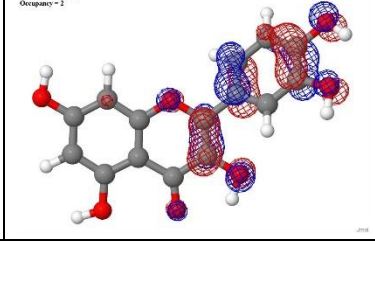
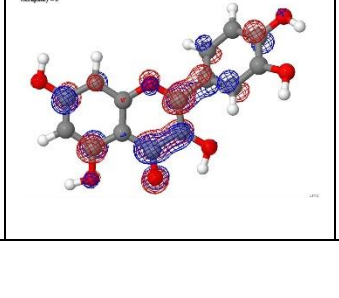
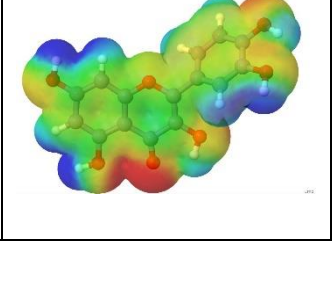
Tangeretin	Attenuating oxidative stress and protecting hepatocellular architecture

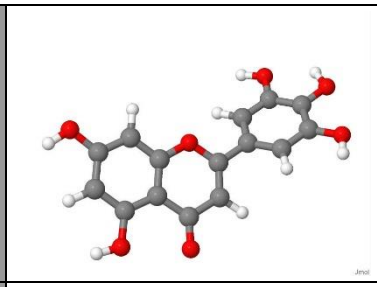
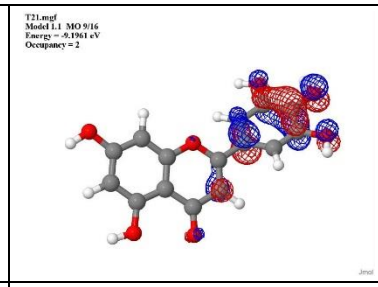
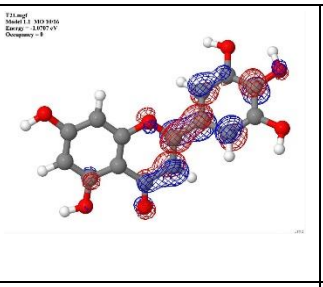
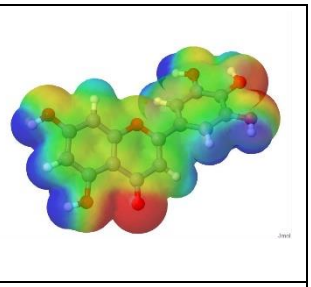
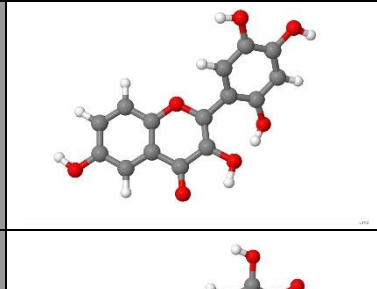
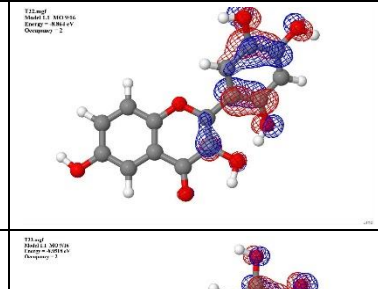
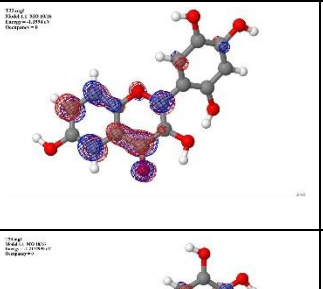
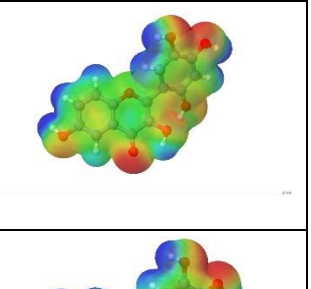
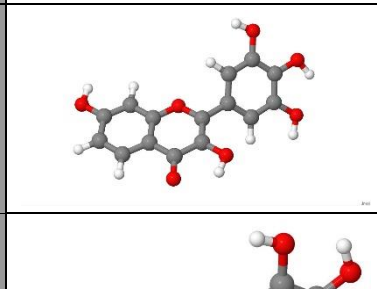
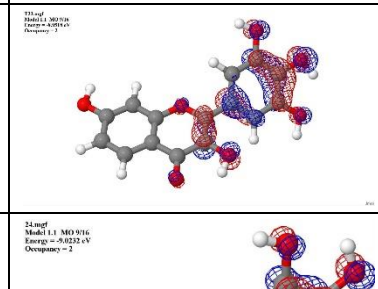
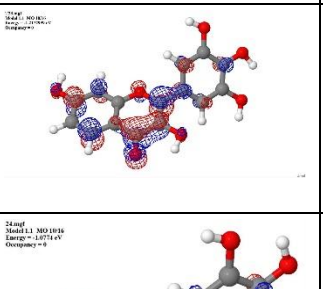
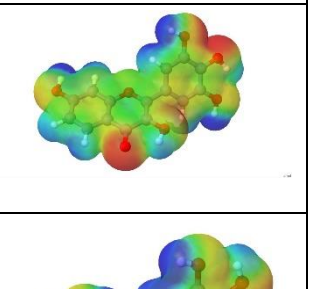
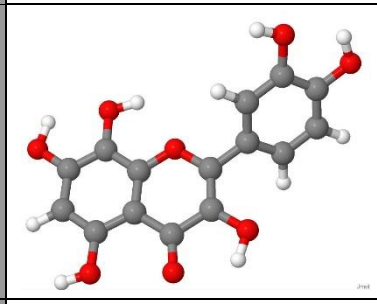
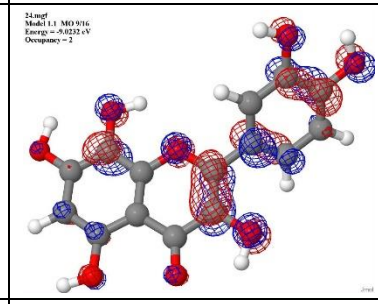
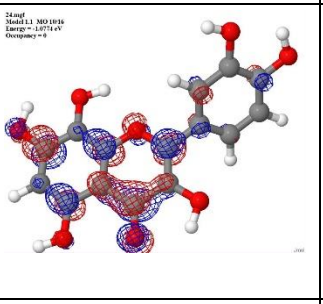
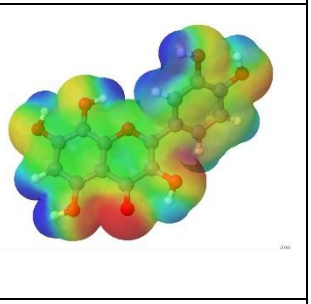
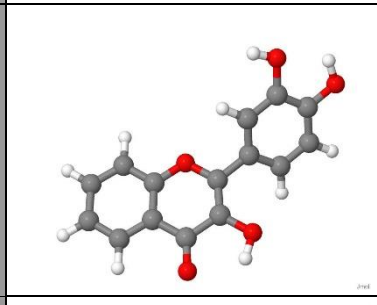
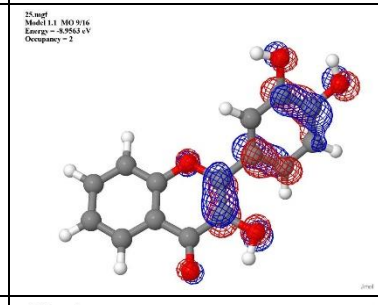
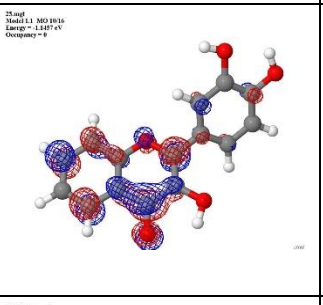
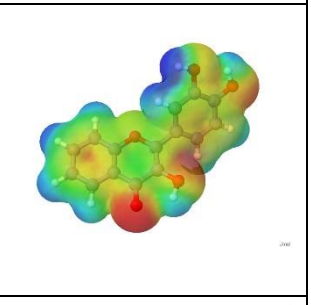
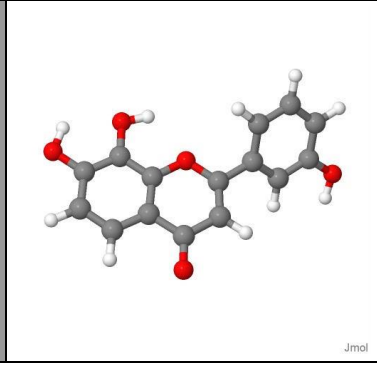
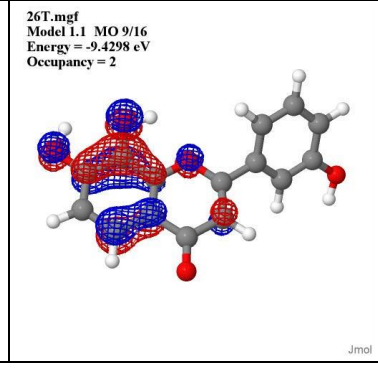
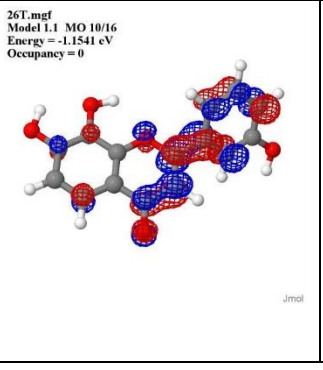
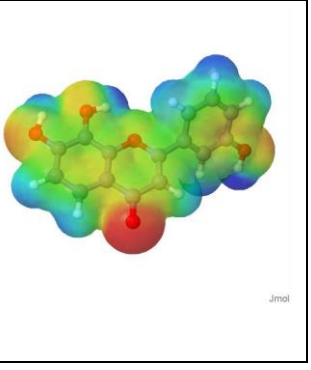
Table 1.20 HOMO, LUMO, and molecular electrostatic potential surface MEPS

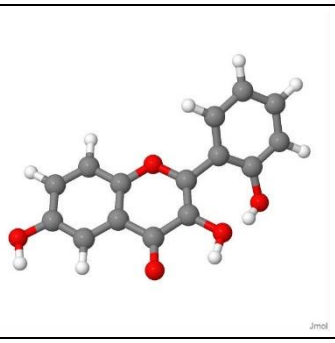
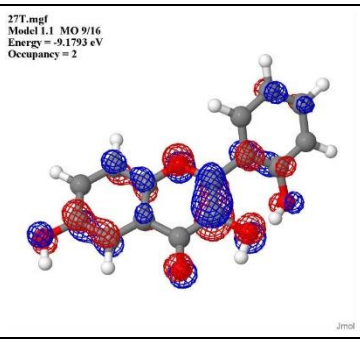
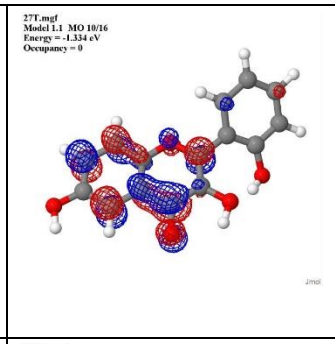
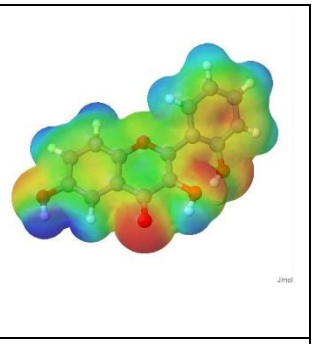
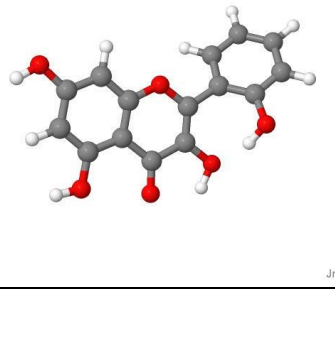
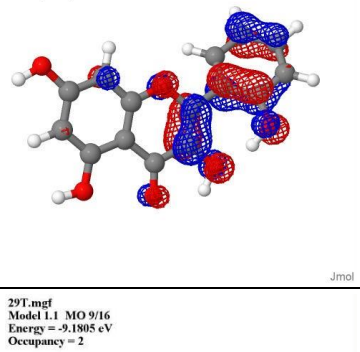
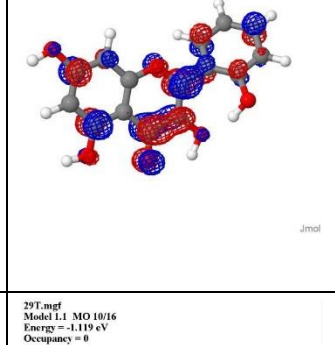
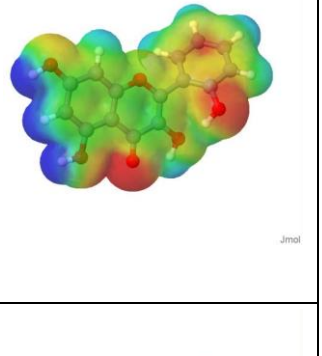
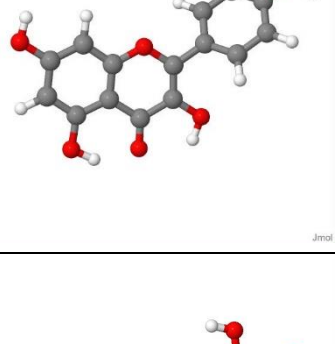
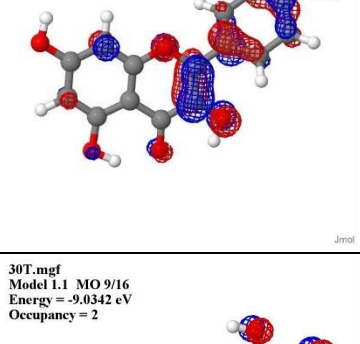
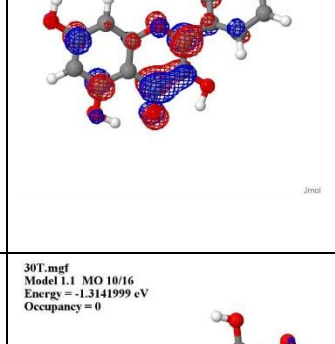
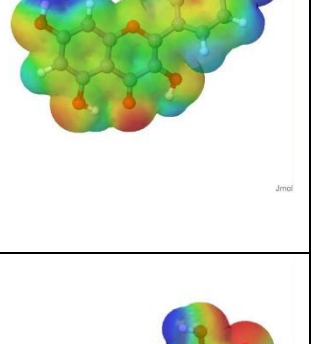
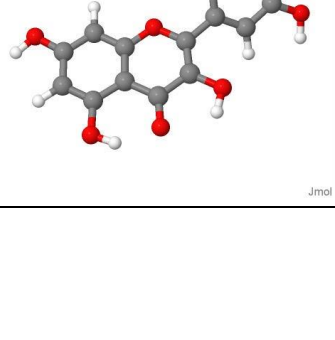
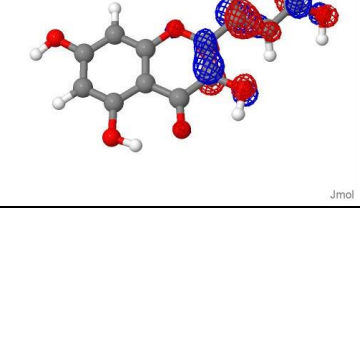
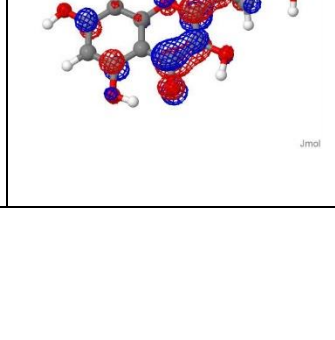
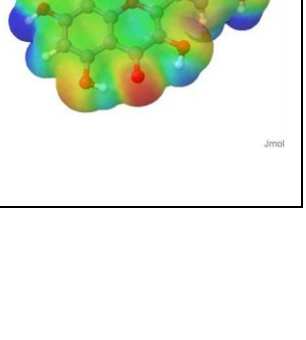
Num	Neutral	HOMO	LUMO	Electrostatic Potential
1				
2				
3				
4				

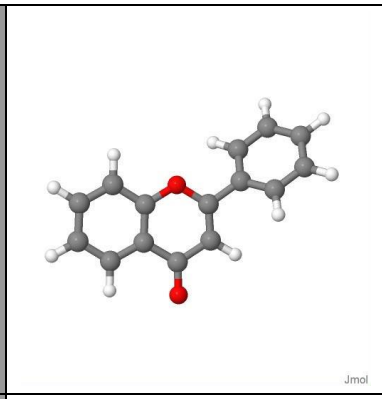
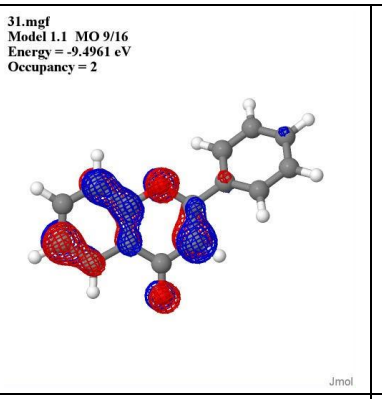
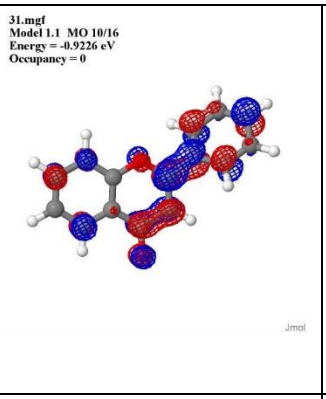
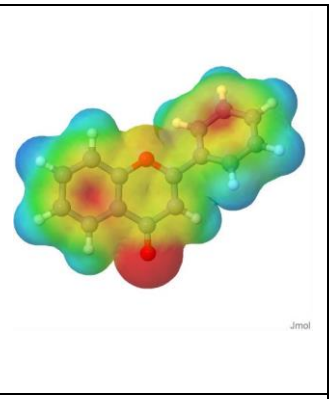
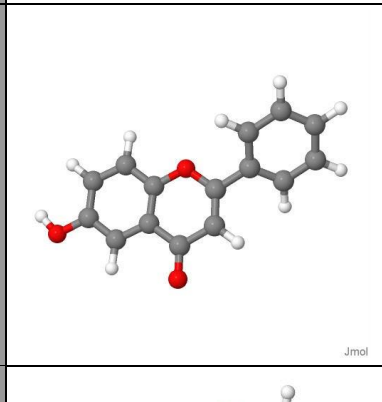
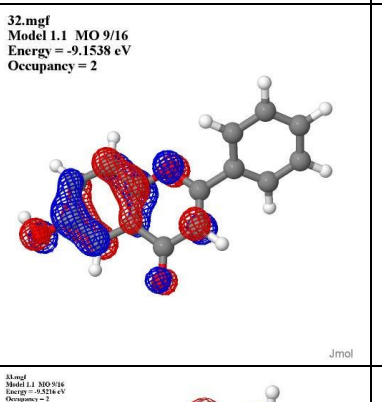
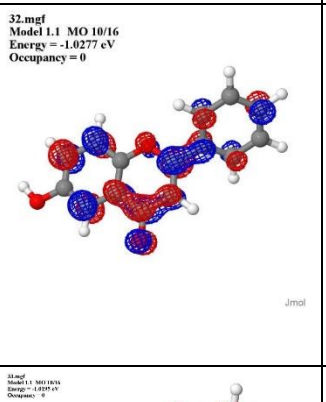
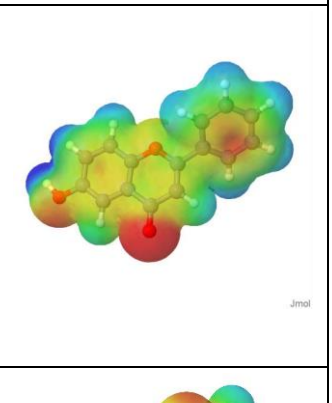
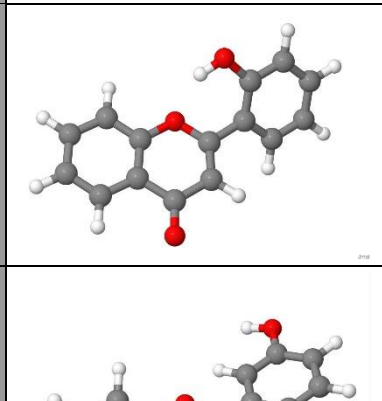
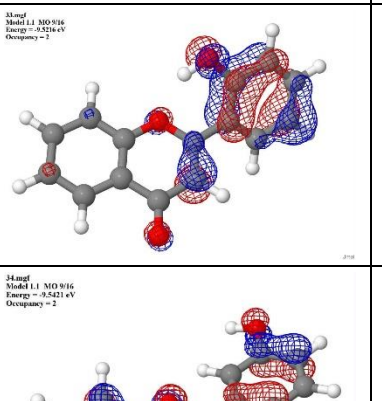
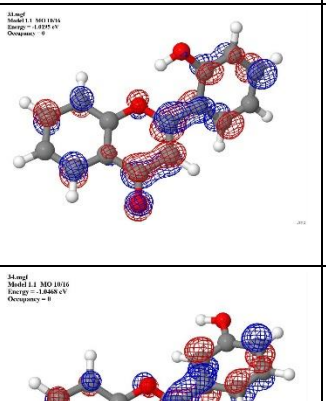
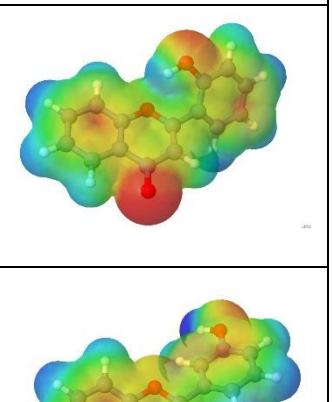
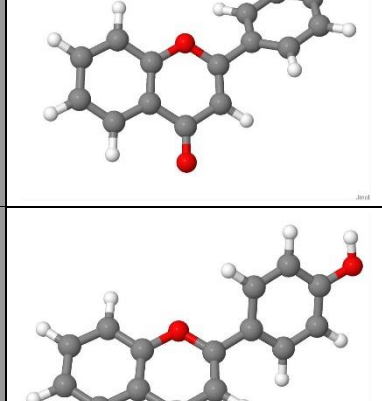
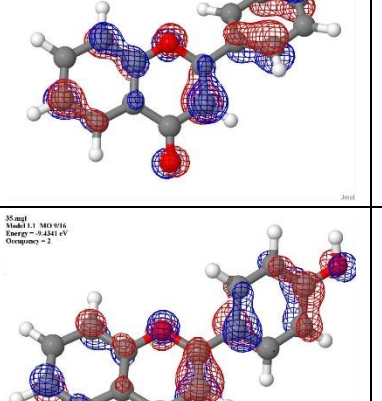
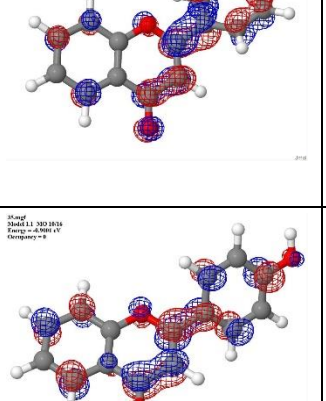
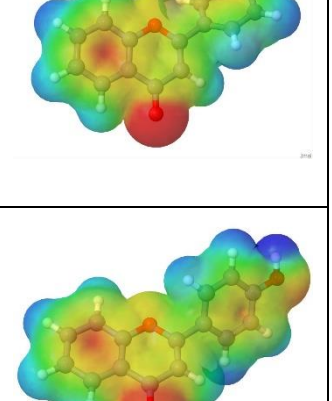
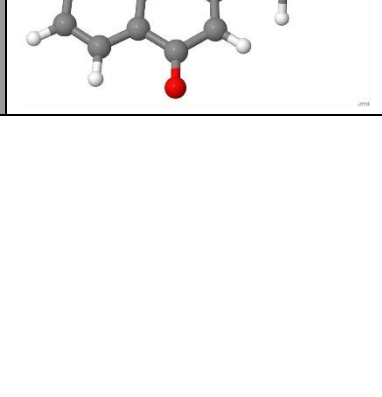
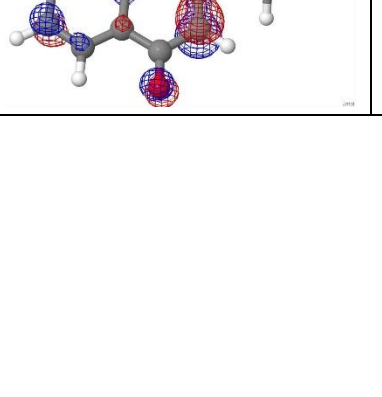
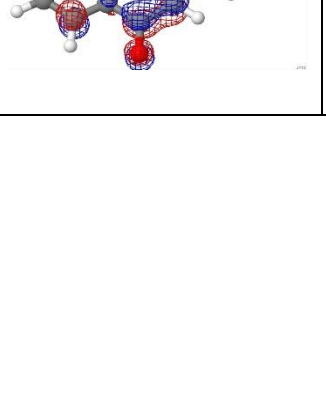
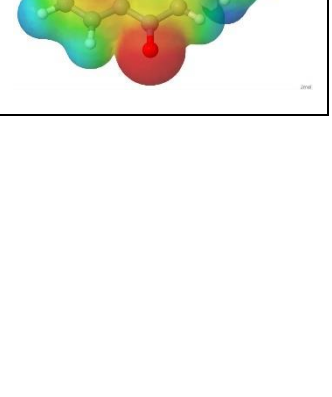
5		 5.mgf Model 1.1 MO 9/16 Energy = -9.1231 eV Occupancy = 2	 5.mgf Model 1.1 MO 10/16 Energy = -1.1626 eV Occupancy = 0	
6		 6.mgf Model 1.1 MO 9/16 Energy = -9.3348 eV Occupancy = 2	 6.mgf Model 1.1 MO 10/16 Energy = -1.0635 eV Occupancy = 0	
7		 7.mgf Model 1.1 MO 8/16 Energy = -9.4144 eV Occupancy = 2	 7.mgf Model 1.1 MO 10/16 Energy = -1.2608 eV Occupancy = 0	
8		 8.mgf Model 1.1 MO 9/16 Energy = -9.228 eV Occupancy = 2	 8.mgf Model 1.1 MO 10/16 Energy = -1.1238999 eV Occupancy = 0	
9		 9.mgf Model 1.1 MO 8/16 Energy = -9.7485 eV Occupancy = 2	 9.mgf Model 1.1 MO 10/16 Energy = -1.0534 eV Occupancy = 0	

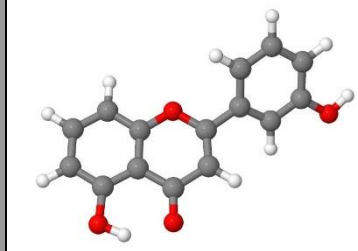
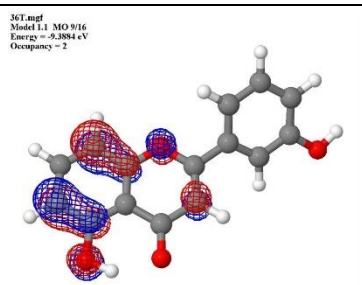
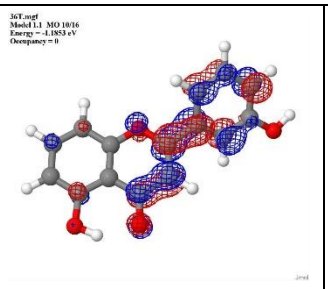
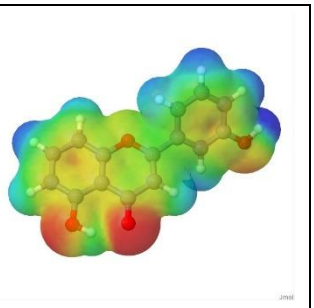
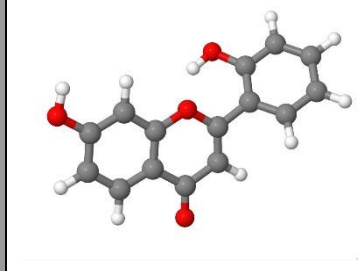
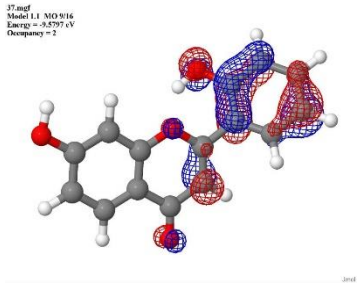
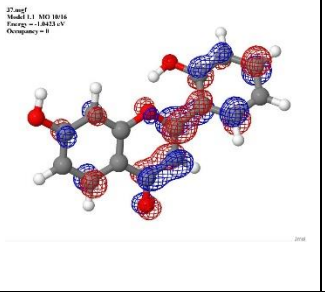
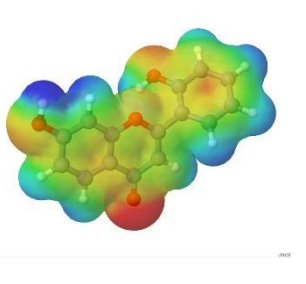
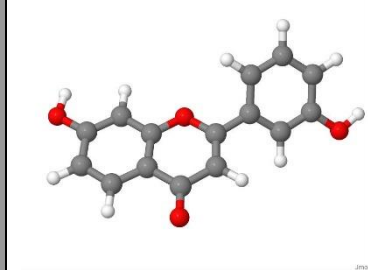
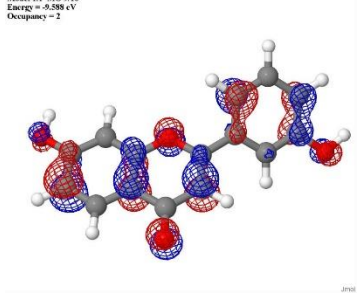
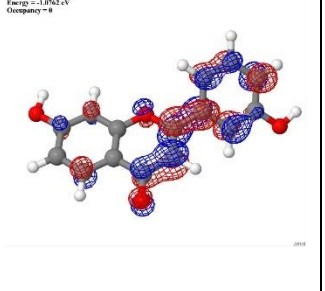
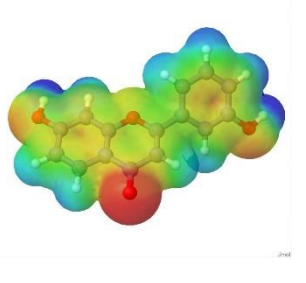
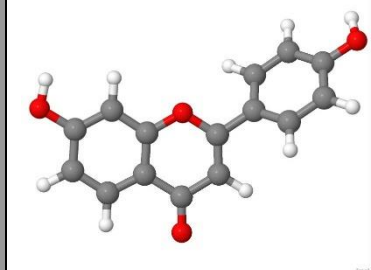
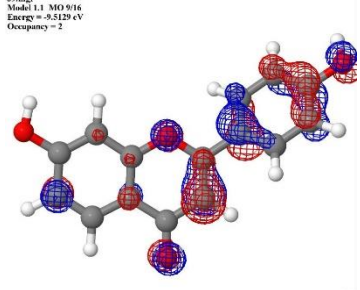
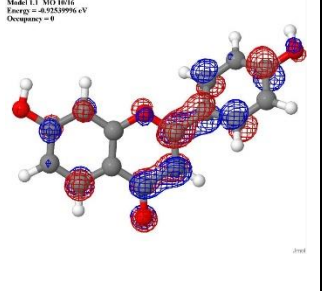
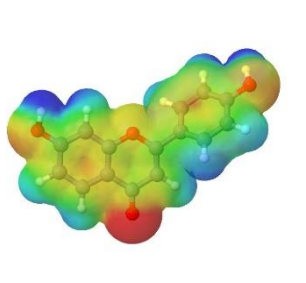
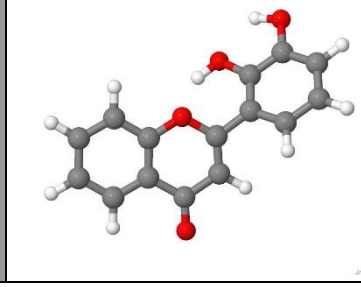
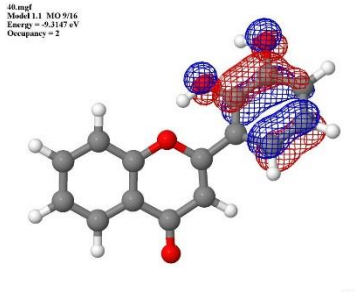
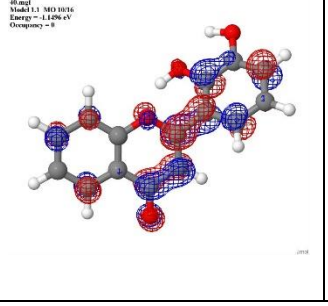
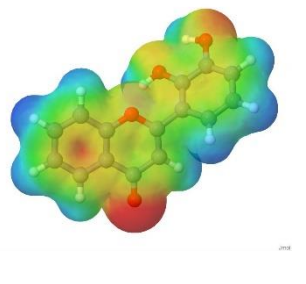
10T				
11				
12				
13				
14				

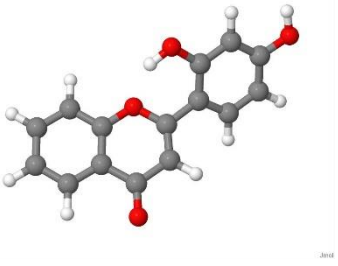
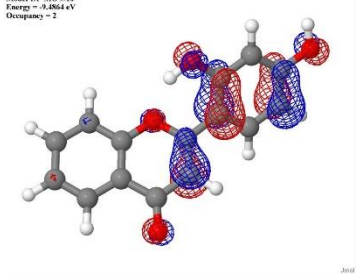
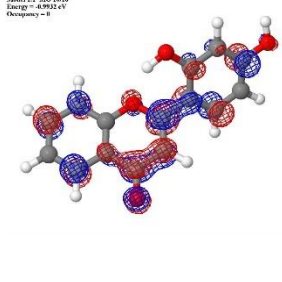
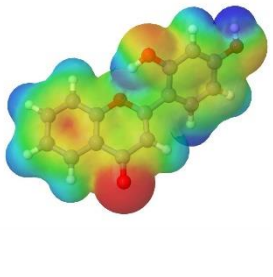
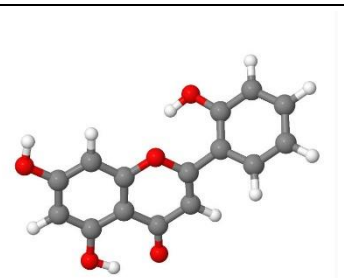
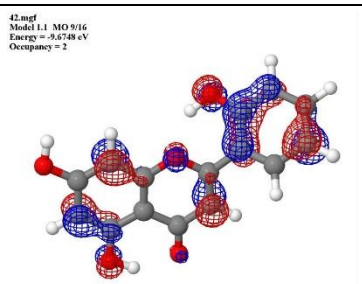
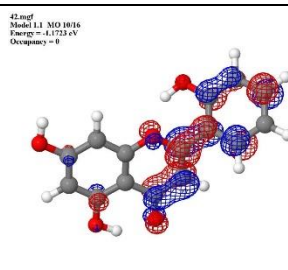
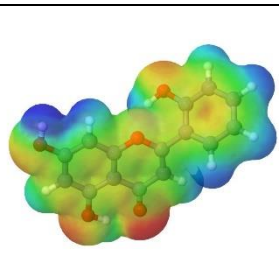
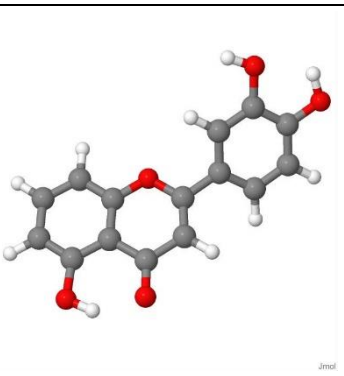
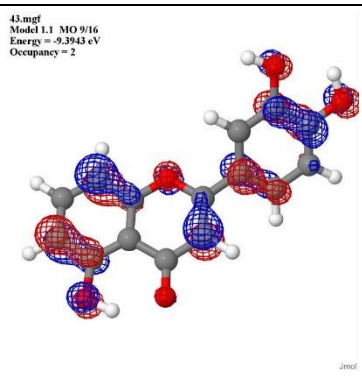
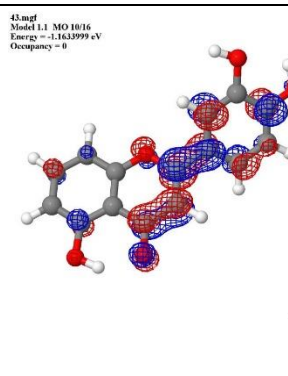
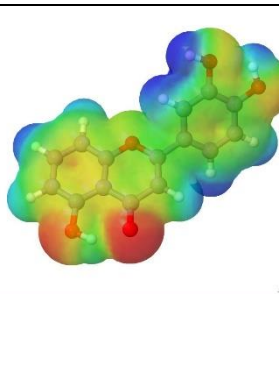
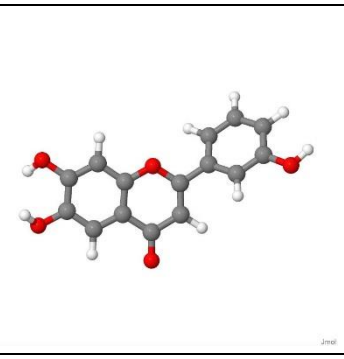
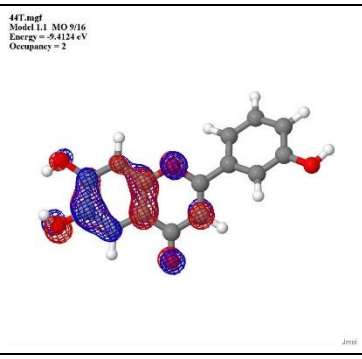
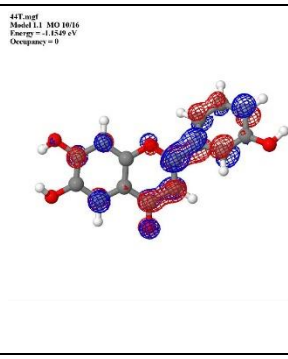
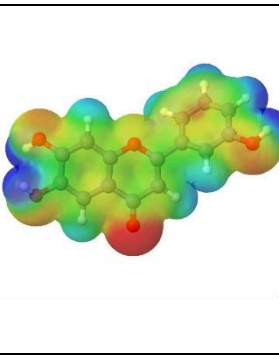
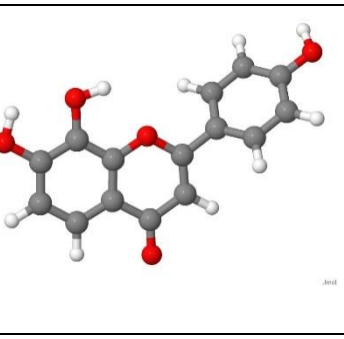
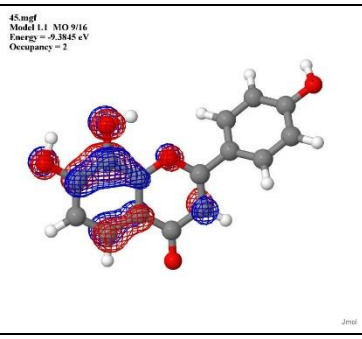
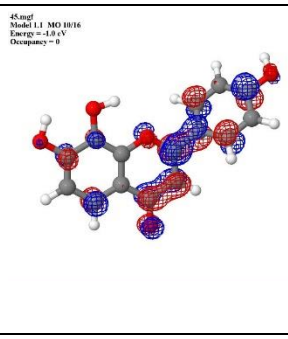
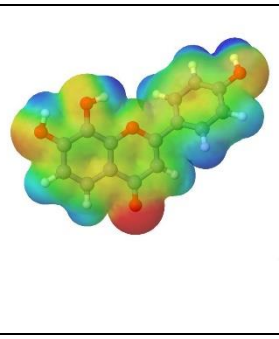
15				
16				
17				
18				
19				
20				

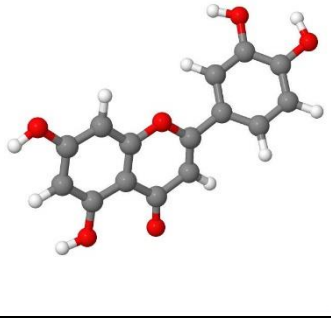
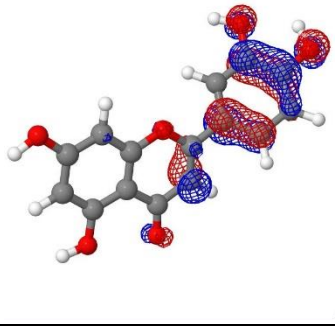
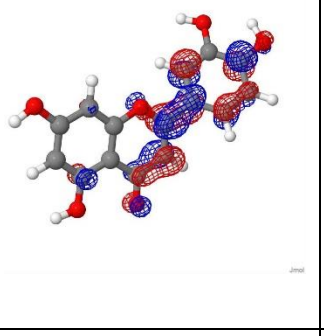
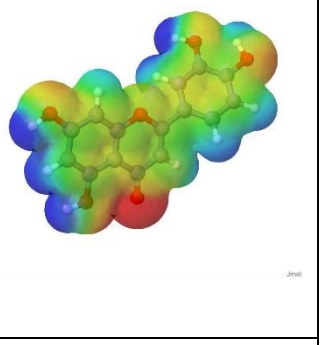
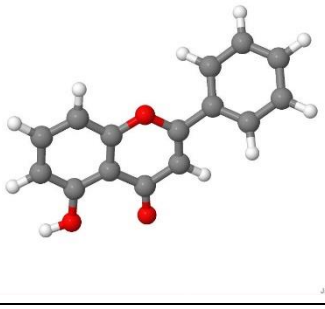
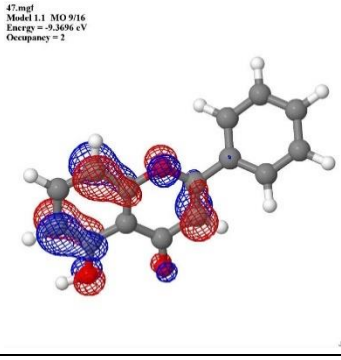
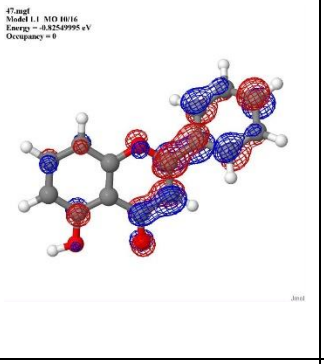
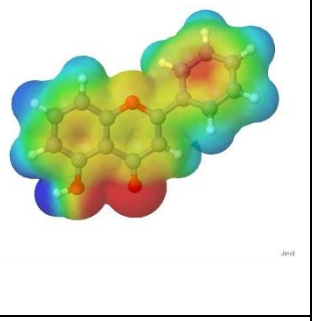
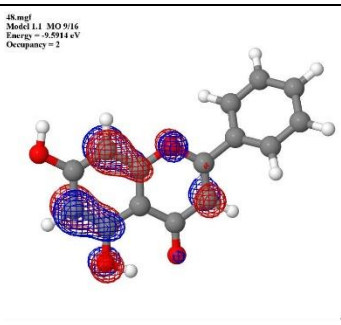
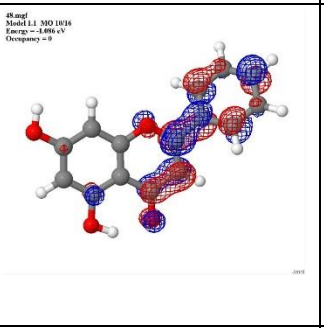
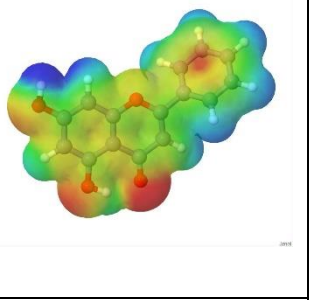
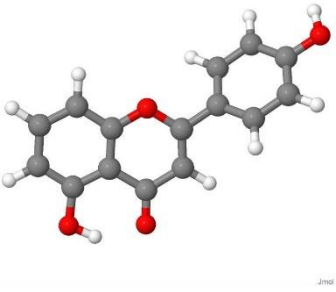
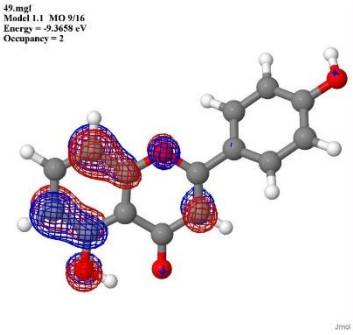
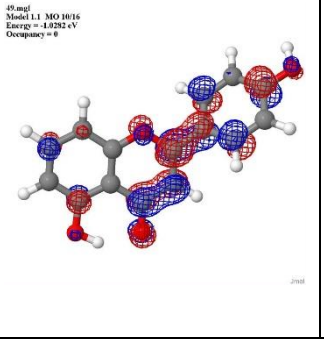
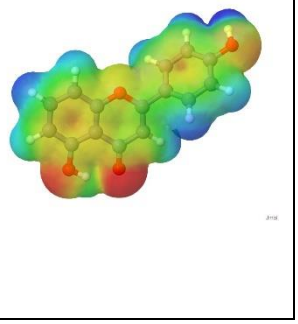
21				
22				
23T				
24T				
25T				
26T				

27T				
28T				
29T				
30T				

31		 31.mgf Model 1.1 MO 9/16 Energy = -9.4961 eV Occupancy = 2	 31.mgf Model 1.1 MO 10/16 Energy = -0.9226 eV Occupancy = 0	
32		 32.mgf Model 1.1 MO 9/16 Energy = -9.1538 eV Occupancy = 2	 32.mgf Model 1.1 MO 10/16 Energy = -1.0277 eV Occupancy = 0	
33				
34				
35				

36T				
37				
38T				
39				
40				

41				
42				
43				
44T				
45				

46		 46.mgf Model 1.1 MO 9/16 Energy = -9.3004 eV Occupancy = 2	 46.mgf Model 1.1 MO 10/16 Energy = -0.9659 eV Occupancy = 0	
47		 47.mgf Model 1.1 MO 9/16 Energy = -9.3696 eV Occupancy = 2	 47.mgf Model 1.1 MO 10/16 Energy = -0.8254/995 eV Occupancy = 0	
48		 48.mgf Model 1.1 MO 9/16 Energy = -9.5914 eV Occupancy = 2	 48.mgf Model 1.1 MO 10/16 Energy = -1.056 eV Occupancy = 0	
49		 49.mgf Model 1.1 MO 9/16 Energy = -9.3658 eV Occupancy = 2	 49.mgf Model 1.1 MO 10/16 Energy = -1.0282 eV Occupancy = 0	

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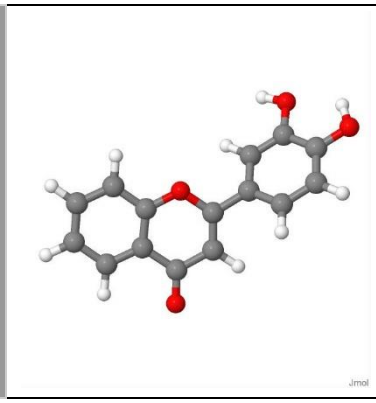

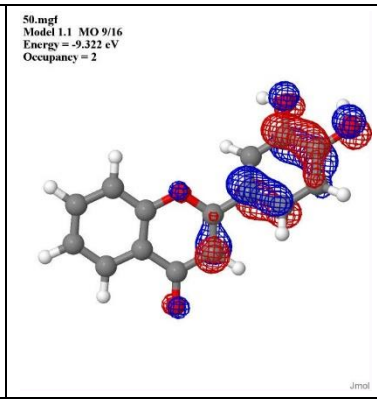
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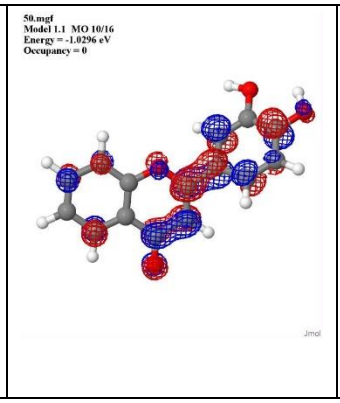
Occupancy = 2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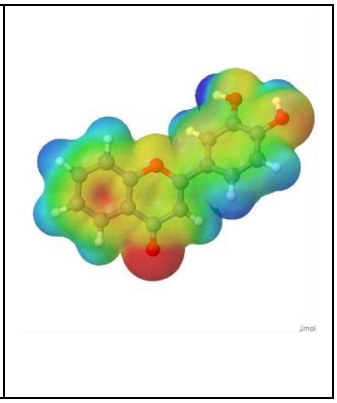
Model 1.1 MO 10/16
Energy = -1.0296 eV
Occupancy = 0



Abstract

Abstract

Polyphenols, particularly Flavonoids have been regarded as one of the largest and most common classes of plant secondary metabolites with important antioxidant properties, correlated with the prevention of cancer as well as other various diseases. This antioxidant activity acts mainly by three mechanisms: Hydrogen Atom Transfer (HAT), Singlet Electron Transfer (SET), and Sequential Proton Loss Electron Transfer (SPLET). Based on a selection of 50 Flavonoid structures and the HAT mechanism, the PM6 and PM7 Semiempirical methods were employed to calculate the Bond Dissociation Energies (BDEs) and five Quantum-Molecular Descriptors: BDE, 1/BDE, HOMO, LUMO, DM, and pLog (1/BDE).

As results, the Quantitative Structure-Activity Relationship (QSAR) Modelling of the experimental antioxidant activity of the 50 flavonoids showed: On one hand, the PM7 semiempirical method could explain the antioxidant activity in function of 5 Quantum-Molecular Descriptors: BDE, 1/BDE, HOMO, LUMO, and pLog (1/BDE) with a correlation coefficient R= 0,796. On the other hand, the PM6 semiempirical could explain the antioxidant activity in function of only 2 descriptors: 1/sBDE and HOMO but with a correlation coefficient R= 0,677. The PM7 model can explain the antioxidant activity better than the PM6 model. A docking test of Flavone, 2'-Hydroyflavone, Remesivir and Chloroquine as SARS-COV2 inhibitors gave the following score trend: Flavone (-7 kcal/mol) = Remdesivir (-7 kcal/mol) > 2'-Hydroyflavone (-6.8 kcal/mol) > Chloroquine (-6.3 kcal/mol)

Keywords: Flavonoids, HAT mechanism, BDE, PM6, PM7, QSAR, Docking.

Résume

Les polyphénols, en particulier les flavonoïdes, ont été considérés comme l'une des classes les plus importantes et les plus courantes de métabolites secondaires végétaux ayant d'importantes propriétés antioxydantes, en corrélation avec la prévention du cancer ainsi que d'autres maladies diverses. Cette activité antioxydante agit principalement par trois mécanismes : le Transfert D'atome D'hydrogène (HAT), le Transfert D'électrons Singulets (SET) et le Transfert D'électrons Séquentiels par perte de protons (SPLET). Sur la base d'une sélection de 50 structures Flavonoïdes et du mécanisme HAT, les méthodes semi-empiriques PM6 et PM7 ont été utilisées pour calculer les énergies de dissociation des liaisons (BDE) et cinq descripteurs quantiques-moléculaires : BDE, 1 / BDE, HOMO, LUMO, DM et pLog (1 / BDE).

Comme résultats, la modélisation Quantitative de la Relation Structure-Activité (QSAR) de l'activité antioxydante expérimentale des 50 Flavonoïdes a montré : D'une part, la méthode semi-empirique PM7 pourrait expliquer l'activité antioxydante en fonction de 5 descripteurs quantiques-moléculaires : BDE, 1 / BDE, HOMO, LUMO et pLog (1 / BDE) avec un coefficient de corrélation R = 0,796. En revanche, le PM6 semi-empirique pourrait expliquer l'activité antioxydante en fonction de seulement 2 descripteurs : 1 / sBDE et HOMO mais avec un coefficient de corrélation R = 0,677. Le modèle PM7 peut mieux expliquer l'activité antioxydante que le modèle PM6. Un test docking de Flavone, 2'-Hydroyflavone, Remesivir et Chloroquine en tant qu'inhibiteurs du SARS-COV2 a donné le score suivant : Flavone (-7 kcal / mol) = Remdesivir (-7 kcal / mol)> 2'-Hydroyflavone (-6,8 kcal / mol)> Chloroquine (-6,3 kcal / mol)

Mots clés : Flavonoïdes, Mécanisme HAT, BDE, PM6, PM7, QSAR, Docking.

ملخص

تعتبر مادة البوليفينول، وخاصة الفلافونويد، واحدة من أكبر وأشهر فئات المستقلبات الثانوية النباتية ذات الخصائص الهامة المضادة للأكسدة، والتي ترتبط بالوقاية من السرطان بالإضافة إلى أمراض مزمنة الأخرى. يعمل هذا النشاط المضاد للأكسدة بشكل أساسي من خلال ثلاث آليات: نقل ذرة الهيدروجين (HAT)، ونقل الإلكترون الفردي (SET)، ونقل الإلكترون المتسلسل لفقدان البروتون (SPLET). بناءً على مجموعة مختارة من 50 بنية فلافونويد وآلية HAT، تم استخدام طرق PM6 و PM7 شبه التجريبية لحساب طاقات تفكك الرابطة (BDEs) وخمسة واصفات جزيئية كمية: BDE، 1/BDE، HOMO، LUMO، DM، وسجل pLog (1 / BDE.)

وكنتيجة، أظهرت النمذجة الكمية للعلاقة بين البنية والنشاط (QSAR) للنشاط التجريبي لمضادات الأكسدة لخمسين فلافونويد: من جهة، يمكن للطريقة شبه التجريبية PM7 أن تشرح نشاط مضادات الأكسدة في وظيفة 5 واصفات جزيئية كمية:BDE / 1 , BDE، HOMO، LUMO، و pLog (1 / BDE) بمعامل الارتباط يقدر ب R = 0.796من جهة أخرى، يمكن أن يفسر PM6 شبه التجريبي نشاط مضادات الأكسدة في وظيفة اثنين فقط من الواصفين: sBDE / 1 و HOMOولكن بمعامل الارتباط يقدر ب R = 0.677.يمكن أن تشرح طريقة PM7 نشاط مضادات الأكسدة بشكل أفضل من طريقة PM6.أعطى اختبار الالتحام لـ Flavone و2'-Hydroyflavone و Remesivirو Chloroquineكمثبطات SARS-COV2 النتيجة التالية: Flavone (-7 kcal / mol) <= Remdesivir (-7 kcal / mol) <= 2'-Hydroyflavone (-6.8)سعرات حرارية / مول)> الكلوروكين (-6.3 كيلو كالوري / مول)

الكلمات الرئيسية: الفلافونويد، آلية HAT، BDE، PM6، PM7، QSARالإرساء.

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Entitled: Computer Aided Drug Design of Novel Active Polyphenols: QSAR Approach

A Thesis Submitted to the Department of Applied Biology in Partial Fulfillment of the Requirements for a Master's Degree in Bioinformatics

Abstract:

Polyphenols, particularly Flavonoids have been regarded as one of the largest and most common classes of plant secondary metabolites with important antioxidant properties, correlated with the prevention of cancer as well as other various diseases. This antioxidant activity acts mainly by three mechanisms: Hydrogen Atom Transfer (HAT), Singlet Electron Transfer (SET), and Sequential Proton Loss Electron Transfer (SPLET). Based on a selection of 50 Flavonoid structures and the HAT mechanism, the PM6 and PM7 Semiempirical methods were employed to calculate the Bond Dissociation Energies (BDEs) and five Quantum-Molecular Descriptors: BDE, 1/BDE, HOMO, LUMO, DM, and pLog (1/BDE).

As results, the Quantitative Structure-Activity Relationship (QSAR) Modelling of the experimental antioxidant activity of the 50 flavonoids showed: On one hand, the PM7 semiempirical method could explain the antioxidant activity in function of 5 Quantum-Molecular Descriptors: BDE, 1/BDE, HOMO, LUMO, and pLog (1/BDE) with a correlation coefficient R= 0,796. On the other hand, the PM6 semiempirical could explain the antioxidant activity in function of only 2 descriptors: 1/sBDE and HOMO but with a correlation coefficient R= 0,677. The PM7 model can explain the antioxidant activity better than the PM6 model. A docking test of Flavone, 2'-Hydroyflavone, Remesivir and Chloroquine as SARS-COV2 inhibitors gave the following score trend: Flavone (-7 kcal/mol) = Remdesivir (-7 kcal/mol) > 2'-Hydroyflavone (-6.8 kcal/mol) > Chloroquine (-6.3 kcal/mol)

Keywords: Flavonoids, HAT mechanism, BDE, PM6, PM7, QSAR, Docking

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