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Review Article

A Review, Inventory Structural Aspects of Phytochemical Compounds in Hawthorn Plant and Highlighting their Properties: Towards Standardization and Authentication

Najoua Soulo[1]*, Iliass Lahmass[2], Nor El houda Tahiri[1,3], Badiaa Lyoussi[1], Zineb Benziane-Ouaritini[1]

[1]*Laboratory of Natural Substances, Pharmacology, Environment, Modeling, Health, and Quality of Life, Faculty of Sciences Dhar El Mahraz, Sidi Mohamed Ben Abdellah University (USMBA) -Fez, Morocco*
[2]*Laboratory of Biotechnology, Environment, Agri-food and Health, Faculty of Sciences Dhar El Mahraz, Sidi Mohamed Ben Abdellah University, B.P 1796 Atlas Fez, Morocco*
[3]*Natural Resources and Sustainable Development Laboratory, Department of Biology, Faculty of Sciences, Ibn Tofail University, P.O. Box 133, Kenitra 14000, Morocco*

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ABSTRACT

In phytotherapy, *Crataegus* (hawthorn) is one of the most remarkable medicinal plants. Recently, it has gained attention for treating diseases mostly affecting the cardiovascular system. The pharmacologically active metabolites that give *Crataegus* its activity are flavonoids, specifically hyperoside, vitexin, and rutin, according to reports. Consequently, the amounts of these active metabolites in phytopharmaceuticals meant to be made from *Crataegus* species are standardized in accordance with those specified by the official pharmacopeias. Scientific databases were the source of the knowledge about hawthorn that was available. The information gathered is summarized in this publication together with information on traditional applications, phytochemistry, pharmacology, and concerns. As indicated by the literature review, *Crataegus* is a polyphyletic genus comprising approximately 3300 species, as demonstrated by phylogenetic and morphological studies. A total of 249 phytochemical compounds have been identified within this genus. These include flavonoids, lignans, fatty acids, organic acids, monoterpenoids, sesquiterpenoids, terpenoids, and steroids, all of which are present in hawthorn. Correlative research on its pharmacological properties and traditional applications is currently lacking. Furthermore, several varieties of hawthorn with traditional uses have not yet been the subject of phytochemical and pharmacological investigation. Consequently, a thorough investigation of the genus *Crataegus* is essential.

Keywords: *Crataegus*, Hawthorn, Traditional applications, Phytochemical compounds, Pharmacological Characteristics.

Introduction

In many parts of the world, the use of herbal remedies can generally be divided into two categories: formal or "official" practices, increasingly supported by scientific research, and popular oral traditions passed down through generations. [1] According to various historical sources, numerous ancient civilizations including the Sumerians, Indians, Egyptians, Chinese, Romans, Greeks, and Arabs used a wide variety of medicinal plants. The Romans and Arabs further developed the knowledge inherited from the Greeks. The ancient Greeks, in particular, are regarded as the forerunners of modern medicine for integrating traditional practices with scientific reasoning. Notable authors such as Galen, Hippocrates, and Dioscorides demonstrated their interest in the medicinal uses of plants through extensive treatises. [2] Medicinal plants from the Rosaceae family are commonly found across the globe. [3] The genus *Crataegus* L. (family Rosaceae) displays chromosomal numbers of 2n = 32; 2n (2x) = 34; and 2n (3x) = 51.[4]

*Corresponding author. E mail: najoua.soulo@usmba.ac.ma
Tel: + 212 671727831

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This genus, widely distributed across Europe, North Africa, and Western Asia, is valued not only for its ornamental appeal but also for its long-standing use in traditional medicine.[5] It is known by various local names in Turkey, such as "halıç," "haziran," "yaban gülü," "ekşi muşmula," "aluç," "alıç," and "yemişen."[6] In Kazakhstan's Ile-Alatau mountains, *Crataegus almaatensis* locally known as "pojark" is found.[7] In Mexico, all *Crataegus* species are referred to as "tejocote" or "manzanita," meaning "little apple."[8]

The name originates from the Nahuatl term *tetl-xocotl*, which means "wild or hard sour fruit."[9] In China, hawthorn is called "Shan Zha,"[10] while in the Middle East, it is known as "Zaarour."[11] In Chile, the local German names include "Peumo," "Peumo Alemán," or "Majuelo."[12] In Morocco, hawthorn is traditionally known as *Za'rur* in Arabic[13] and *Admam* in Amazigh.[14]

Hawthorn has been used for medicinal purposes since Roman times.[15] Dioscorides was the first to describe *Crataegus* as a "cardiotonic" agent in the first century.[16] In *The Compendium of Materia Medica* (*Bencao Gangmu*), a renowned reference in Traditional Chinese Medicine, dried *Crataegus* fruit was prescribed for conditions such as hemafecia, postpartum blood stasis, hernia, cardiodynia, and dyspepsia.[17] Clinical studies have shown that hawthorn extract may enhance exercise tolerance, offer cardioprotective effects, and help prevent myocardial dysfunction in patients with New York Heart Association (NYHA) class II heart failure.[18] Its fruits and flowers are officially listed as cardiovascular agents in the eleventh edition of the Russian Pharmacopoeia.[19] Most pharmacological studies on hawthorn focus on extracts from its leaves and flowers.[20] In both China and Europe, it is commonly consumed and processed into commercial products such as wine, jams, and candies.[21]

The authenticity and quality control of herbal products are major concerns for consumers, regulatory authorities, and manufacturers. To ensure consumers receive products that are safe, effective, and consistent, current Good Manufacturing Practice (CGMP) guidelines for dietary supplements emphasize the accurate identification of botanical ingredients and the evaluation of product potency. [22]

Among the 56 genotypes of *Crataegus* spp. collected from different regions of Iran, the predominant phenolics in the flower extracts were rutin, chlorogenic acid, and hyperoside. A comparative study between the endemic Kazakh species *C. almaatensis Pojark* and the well-known *C. oxyacantha* revealed that the flowers of *C. almaatensis* had a polyphenol content comparable to that of *C. oxyacantha*. [23]

Since antiquity, medicinal plants have been used to treat a broad range of ailments, either on their own or as part of herbal mixtures and dietary supplements. According to modern global quality standards, the effectiveness of these treatments is closely linked to their content of bioactive compounds highlighting the importance of chemical standardization for regulatory approval. [24]

The phytochemical structure of hawthorn

With over 8,000 unique compounds, polyphenols constitute the largest and most thoroughly researched class of plant-derived specialized metabolites. [25] These polyphenolic substances are often grouped together due to their shared structural characteristics and similar biological activities. In many biological investigations, the total polyphenol content is routinely measured as a marker of biological effect. As a result, polyphenols are considered crucial raw materials for extraction, particularly in the production of pharmaceuticals and health-related products.

The structural complexity of polyphenols, combined with the intricate architecture of plant cell walls, necessitates tailoring extraction methods to each plant species. Rapid progress in extraction technologies has facilitated the development of novel approaches designed to enhance both yield and selectivity. [25]

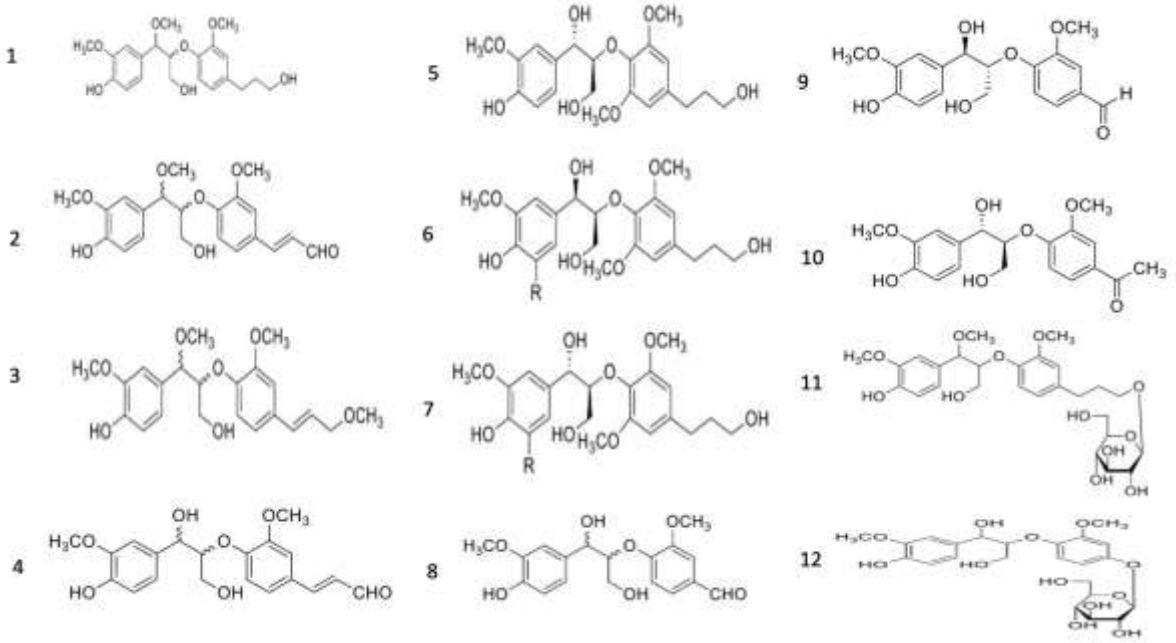
Chemical studies on hawthorn have revealed a broad spectrum of bioactive constituents, including phenolic acids, quercetin, pyrocatechin, terpenoids, lignans, steroids, and organic acids. [26] Among these, lignans a distinct subgroup of polyphenolic compounds have attracted significant interest due to their wide range of biological effects, such as modulating immune responses and regulating cellular signaling pathways.

Lignans

Lignans, a broad class of naturally occurring compounds, are synthesized through the shikimic acid biosynthetic pathway. [27] These compounds are typically classified as secondary metabolites formed by the oxidative dimerization of phenylpropanoid units. [28] Usually, lignans consist of two phenylpropanoid units linked at the β and β' carbon positions and may be connected to other molecules via ether, carbon, or lactone bonds. [29]

There is considerable individual variation in the absorption, bioconversion, and subsequent metabolism of plant lignans into mammalian lignans. In plants, lignans can exist either as aglycones (without sugar moieties) or as glycosides (attached to sugars). To date, secoisolariciresinol is the only lignan oligomer identified in flaxseed. Lignan glycosides are absorbed in the gastrointestinal tract after being converted by intestinal microbiota into enterolignans, specifically enterodiol and enterolactone, as well as lignan aglycones. The degree of hydrolysis required to release lignans from sugars and oligomers in flaxseed, along with the production and bioavailability of enterolignans, varies significantly between individuals. [30]

So far, 95 lignans have been identified and extracted from hawthorn (Figure 1). These compounds are primarily known for their potent anti-inflammatory, anti-aging, antidiabetic, antibacterial, immunomodulatory, cardioprotective, hepatoprotective, anticancer, and antioxidant effects. [31] Additionally, some lignans have demonstrated cytotoxic and antiviral activities against HIV, along with positive impacts on the central nervous system and overall physical performance. [32]



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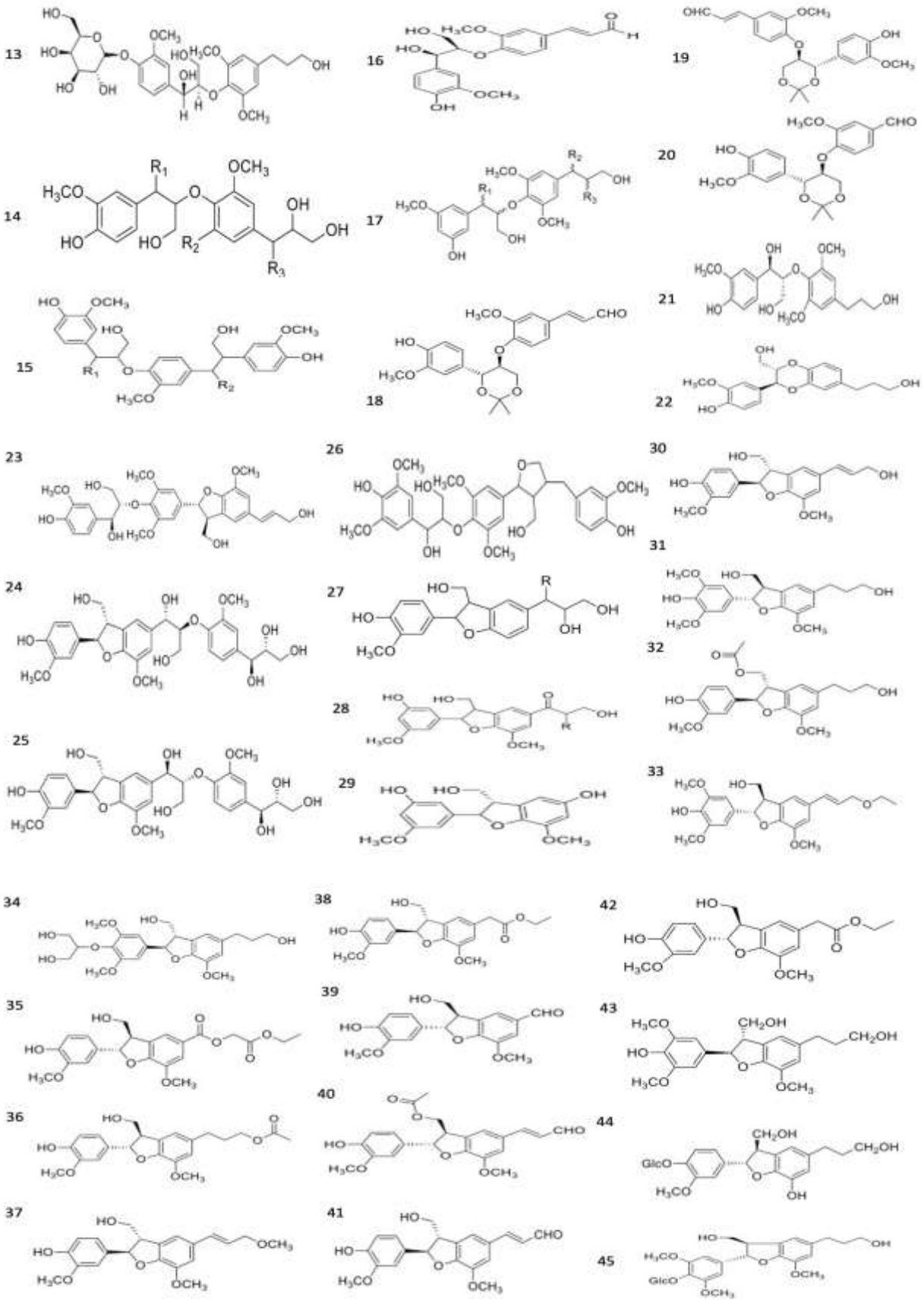

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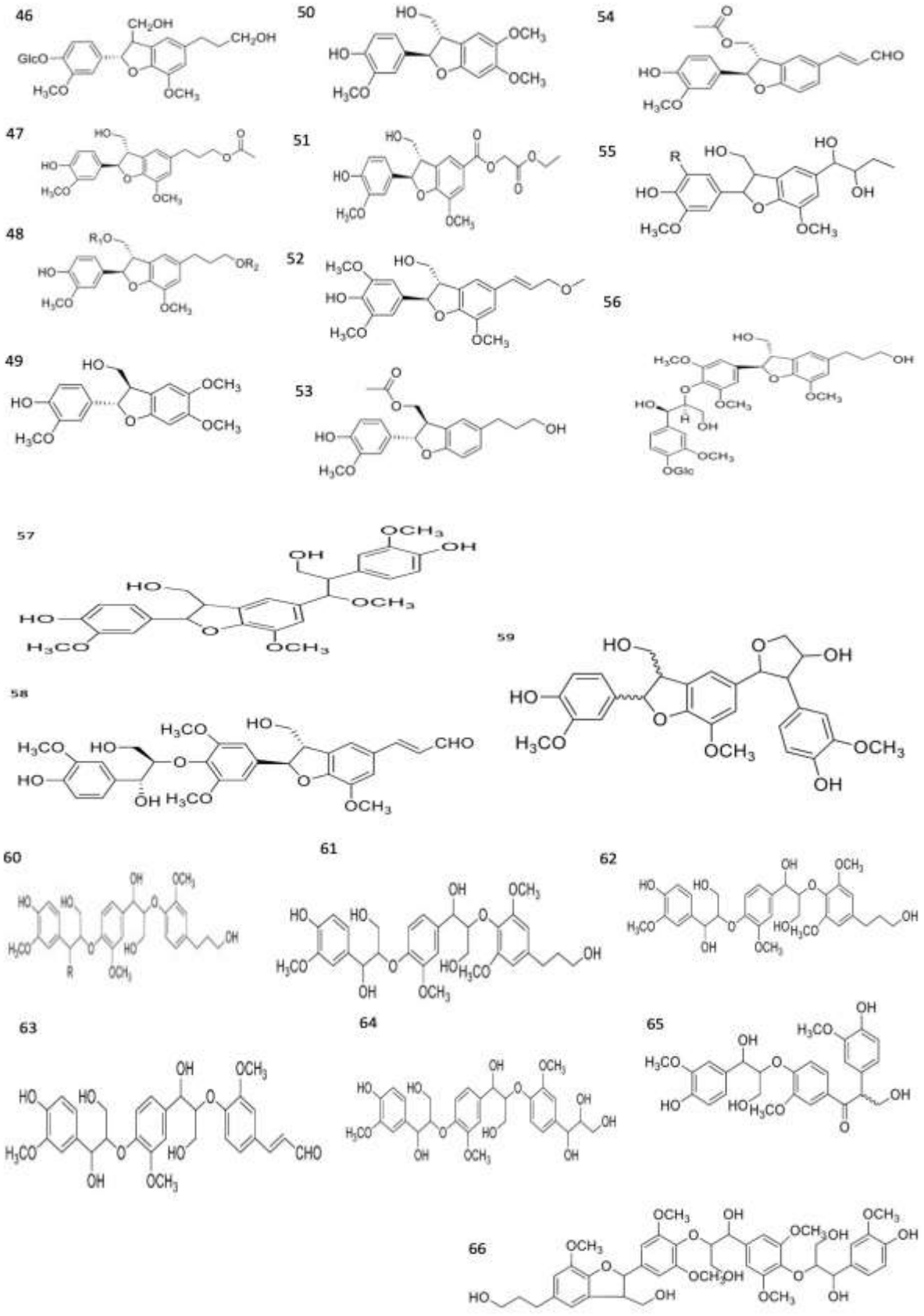

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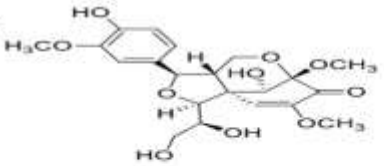

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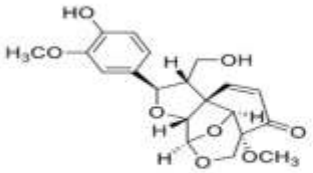

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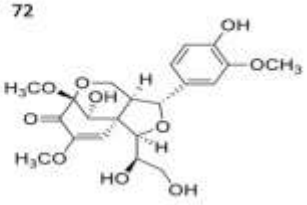

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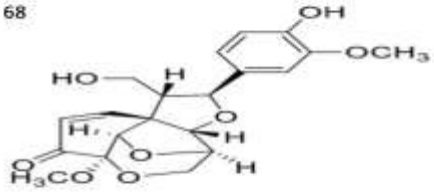

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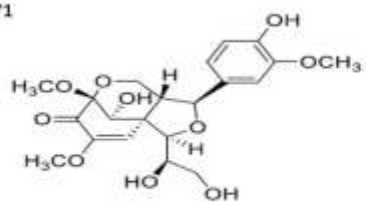

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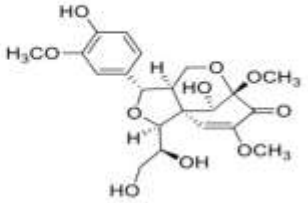

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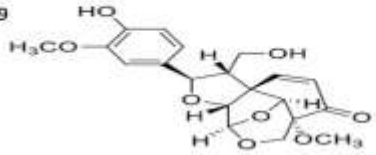

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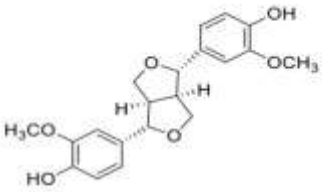

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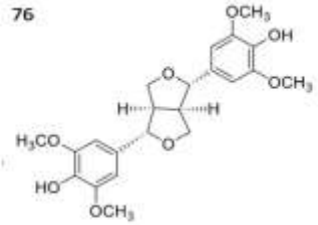

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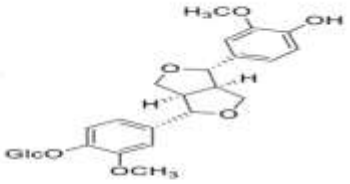

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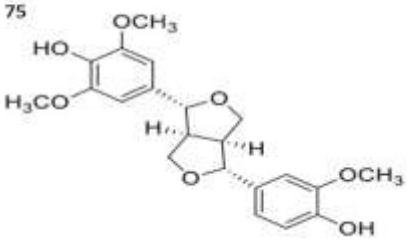

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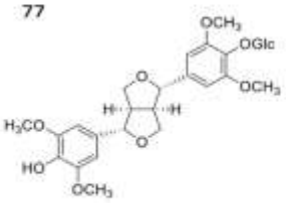

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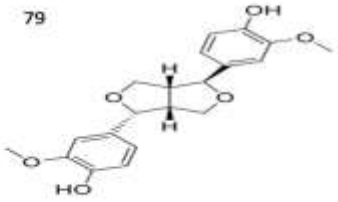

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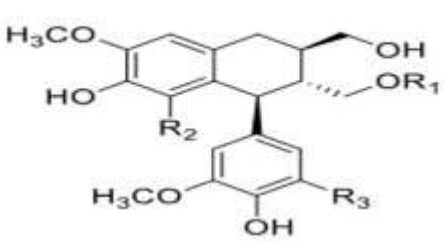

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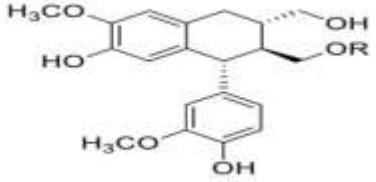

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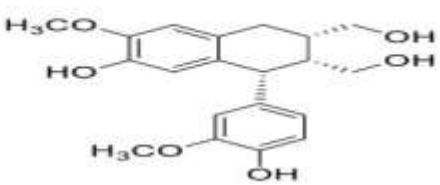

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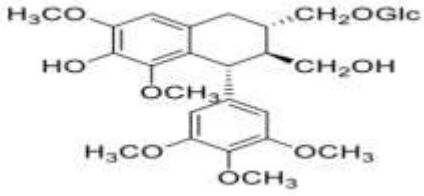

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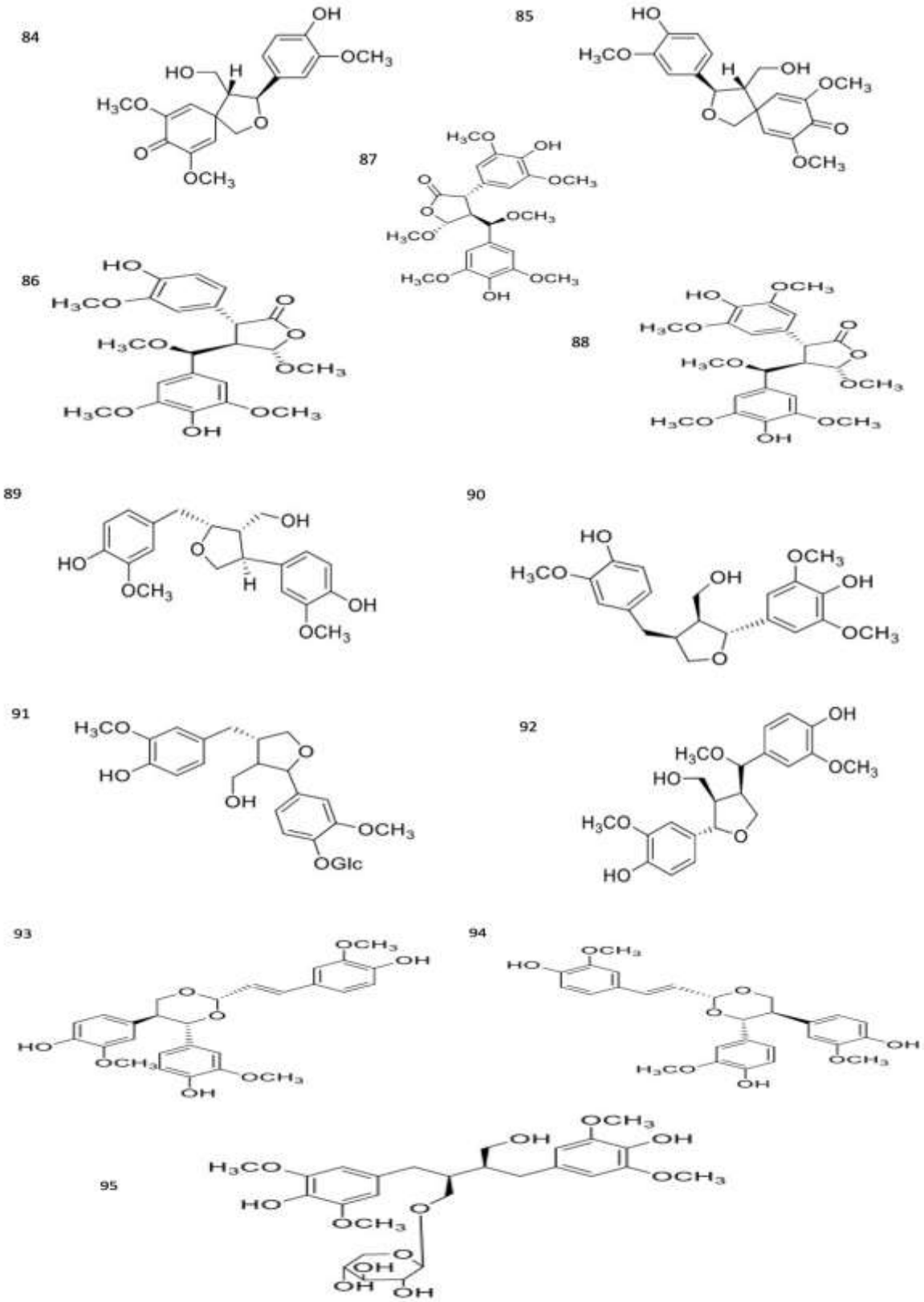

Figure 1: Structures of the lignans separated from hawthorn: (1–22) 8-*O*-4′ neolignans; (23–59) benzofuran neolignans; (60–66) sesquineolignans; (67–73) spirocyclohexenone neolignans; (74–79) 2,6-diarylfurofurans; (80–83) arylnaphthalenes; (84–88) monoepoxy lignans; (89–92) 2-aryl-4-benzyltetrahydrofurans; (93) (+)-Crataegusanoid; (94) (–)-Crataegusanoid B; (95) Ssioriside. [33]

Structures of Terpenoids isolated from hawthorn

Terpenoids comprise a significant portion of the secondary metabolites found in plants. At high temperatures, these compounds are likely to decompose into isoprene (C_5H_8), which is derived from five-carbon precursors, also referred to as isoprene units. Monoterpenes ($C_{10}H_{16}$), sesquiterpenes ($C_{15}H_{24}$), diterpenes ($C_{20}H_{32}$), sesterterpenes ($C_{25}H_{40}$), and triterpenes ($C_{30}H_{48}$) are part of a hierarchical sequence of terpenes formed by the combination of isoprene units, ranging from five-carbon hemiterpenes to forty-carbon tetraterpenes.[34]

Monoterpenoids and sesquiterpenoids

Monoterpenes, which are C_{10} compounds, are composed of two isoprene units that make up natural isoprenoid molecules. [35] These two isoprene units can be organized in either cyclic or acyclic (monocyclic or bicyclic) configurations to form monoterpenes. Their oxygenated counterparts, called monoterpenoids, also contain these units and give rise to a range of chemical configurations. [36] Monoterpenes are widely used in various industries due to their biological activity and aromatic properties. Several monoterpenes are essential in medicine because of their analgesic, antimicrobial, and anti-inflammatory qualities. [37] (Figure 2) represents all the structures of monoterpenoids and sesquiterpenoids extracted from hawthorn.

Terpenoids and steroids

Figure. 3, shows the diversity of all terpenoids and steroids. With a parent nucleus of thirty carbon atoms polymerized from six isoprene units, terpenoids have demonstrated various biological activities, including anticancer, anti-obesity, anti-neuroinflammatory, antibacterial, and antiallergic properties. [38]

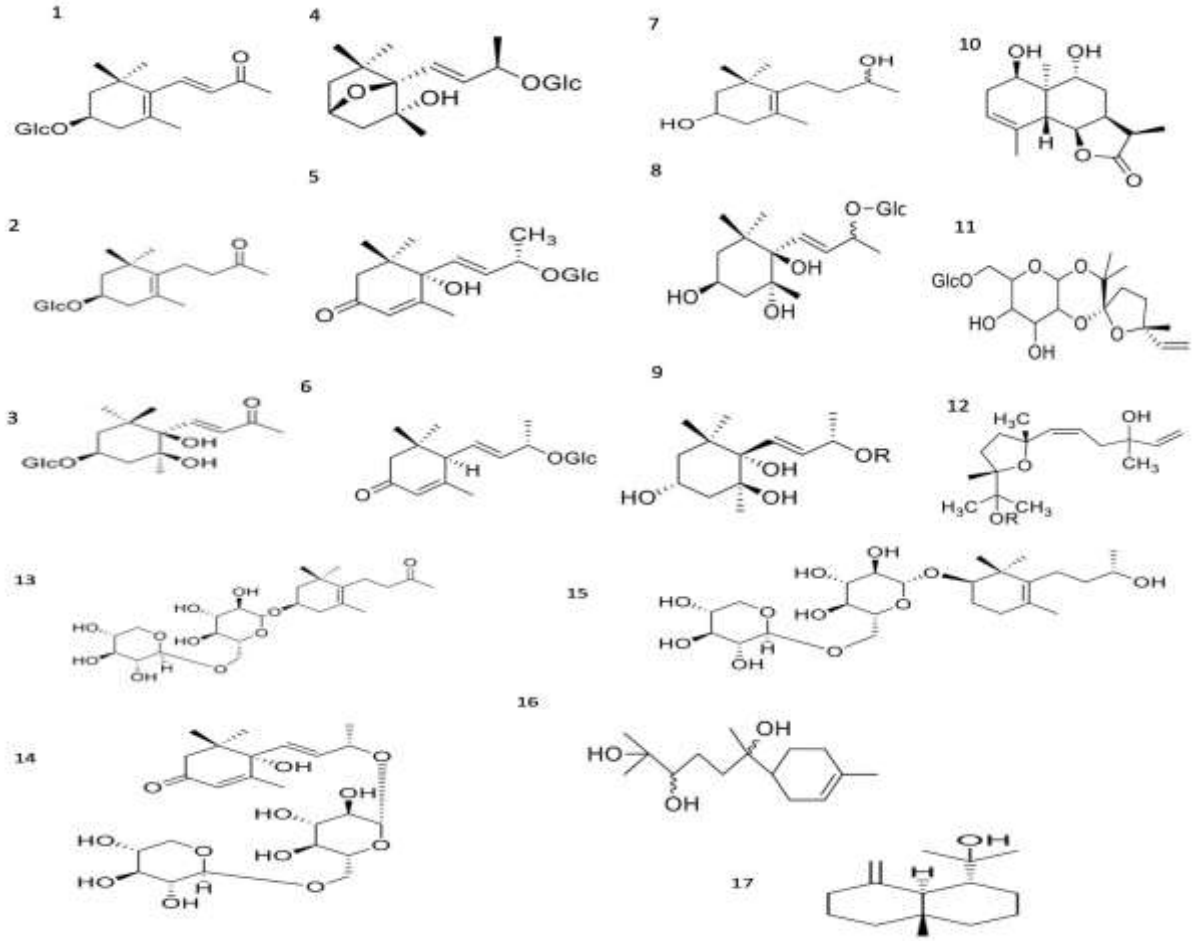

Figure 2: Monoterpenoids and sesquiterpenoids extracted from hawthorn: (1) 3*β*-Glucopyranosyloxy-*β*-ionone; (2) Icariside B6; (3) Pisumionoside; (4) (3S,5R,6R,7E,9R)-3,6-Epoxy-7-megastigmen-5,9-diol-9-*O*-*β*-D-glucopyranoside; (5) (6S,7E,9R)-Roseoside; (6) (6R,9R)-3-Oxo-α-ionol-9-*O*-*β*-D-glucopyranoside; (7) 3,9-Dihydroxymegastigma-5-ene; (8) (3S,5R,6R,7E)-Megastigmane-7-ene-3-hydroxy-5,6-epoxy-9-*O*-*β*-D-glucopyranoside; (9) (3R,5S,6S,7E,9S)-Megastigmane-7-ene-3,5,6,9-tetrol-9-*O*-*β*-D-glucopyranoside; (10) 4-[4*β*-*O*-*β*-D-xylopyranosyl-(1″→6′)-*β*-D-glucopyranosyl-2,6,6-trimethyl-1-cyclohexen-1-yl]-butan-2-one; (11) 1*β*,9α-Dihydroxyeudesm-3-en-5*β*,6α,7α,11α-H-12,6-olide; (12) 5-Ethenyl-2-[2-*O*-*β*-D-glucopyranosyl-(1″→6′)-*β*-D-glucopyranosyl-propan-2-yl]-5-methyltetrahydrofuran-2-ol; (13) (5Z)-6-[5-(2-Hydroxypropan-2-yl)-2-methyltetrahydrofuran-2-yl]-3-methylhexa-1,5-dien-3-ol; (14) (3R,5S,6S,7E,9S)-Megastigmane-7-ene-3,5,6,9-tetrol; (15) (3S,9R)-3,9-Dihydroxymegastigmane-5-one-3-*O*-primeveroside; (16) α-Tetrahydrobisabolen-2,5,6-triol; (17) (1α,4a*β*,8aα)-1-Isopropanol-4a-methyl-8-methylenedecahydronaphthalene.

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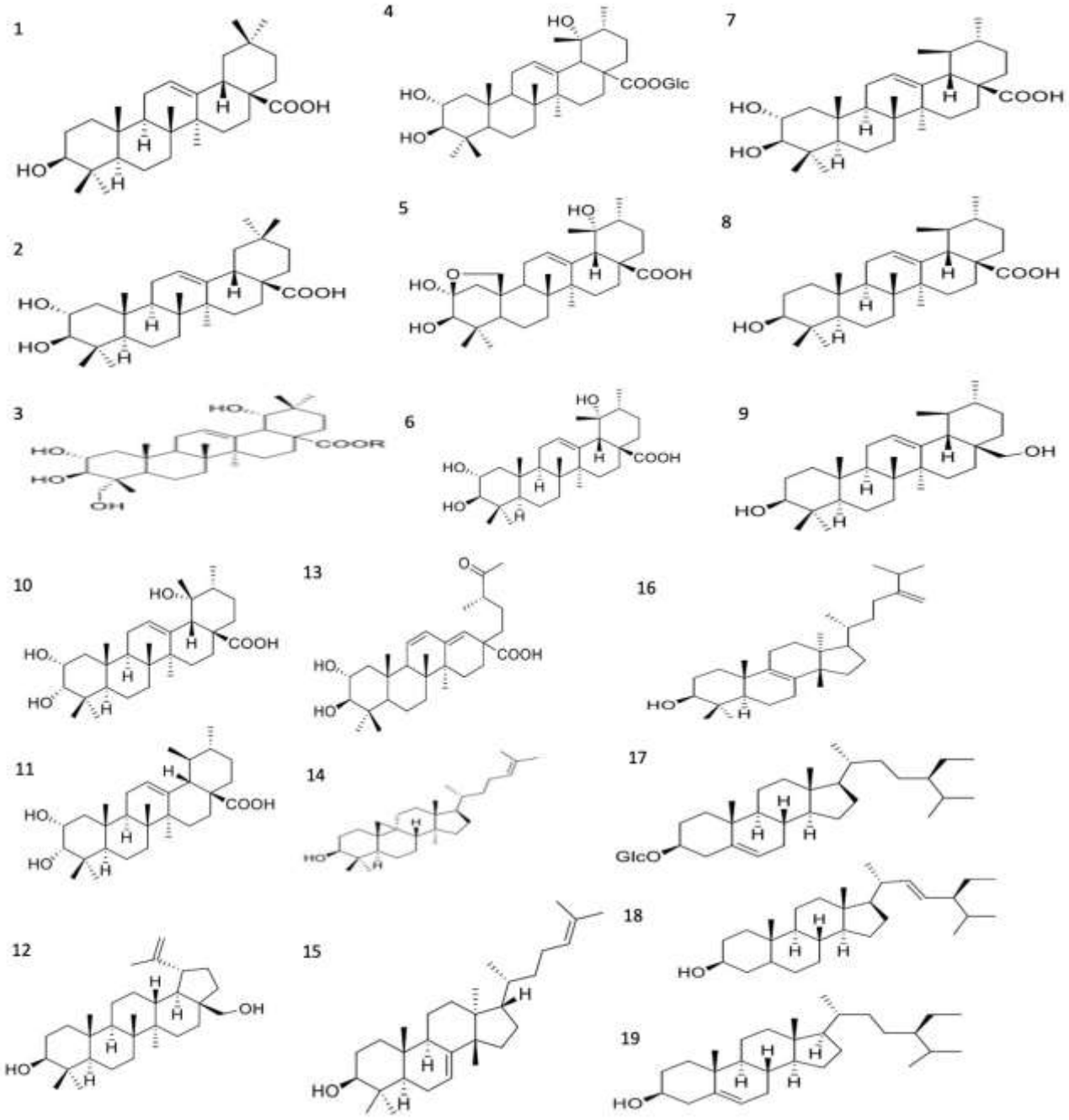

Figure 3: Terpenoids and steroids: (1) Oleanolic acid; (2) Maslinic acid; (3) Arjungenin; (4) Tormentic acid-28-*O*-*β*-D-glucopyranoside; (5) Cuneataol; (6) 2α,3*β*,19α-Trihydroxyursolic acid; (7) Corosolic acid; (8) Ursolic acid; (9) Uvaol; (10) Euscapic acid; (11) 3-Epicorosolic acid; (12) Betulin; (13) 18,19-seco-2α,3*β*-dihydroxy-19-oxo-urs-11,13(18)-dien-28-oic acid; (14) Cycloartenol; (15) Butyrospermol; (16) 24-Methylene-24-dihydrolanosterol; (17) Daucosterol; (18) Stigmosterol; (19) *β*-Sitosterol.

Structures of fatty acids and organic acids isolated from hawthorn

Lipids consist of aliphatic monocarboxylic acids known as fatty acids. These fatty acids are classified as saturated, monounsaturated, or polyunsaturated depending on the number of double bonds they contain. Their carbon chains generally range from four to twenty-eight atoms in length. Although fatty acids can exist in a free form, they are mainly found in seeds and seed oils, where they are incorporated into more complex molecules primarily triglycerides through ester or amide linkages[39]. Figure 4 shows the structures of fatty acids and organic acids that were isolated from hawthorn. [39]

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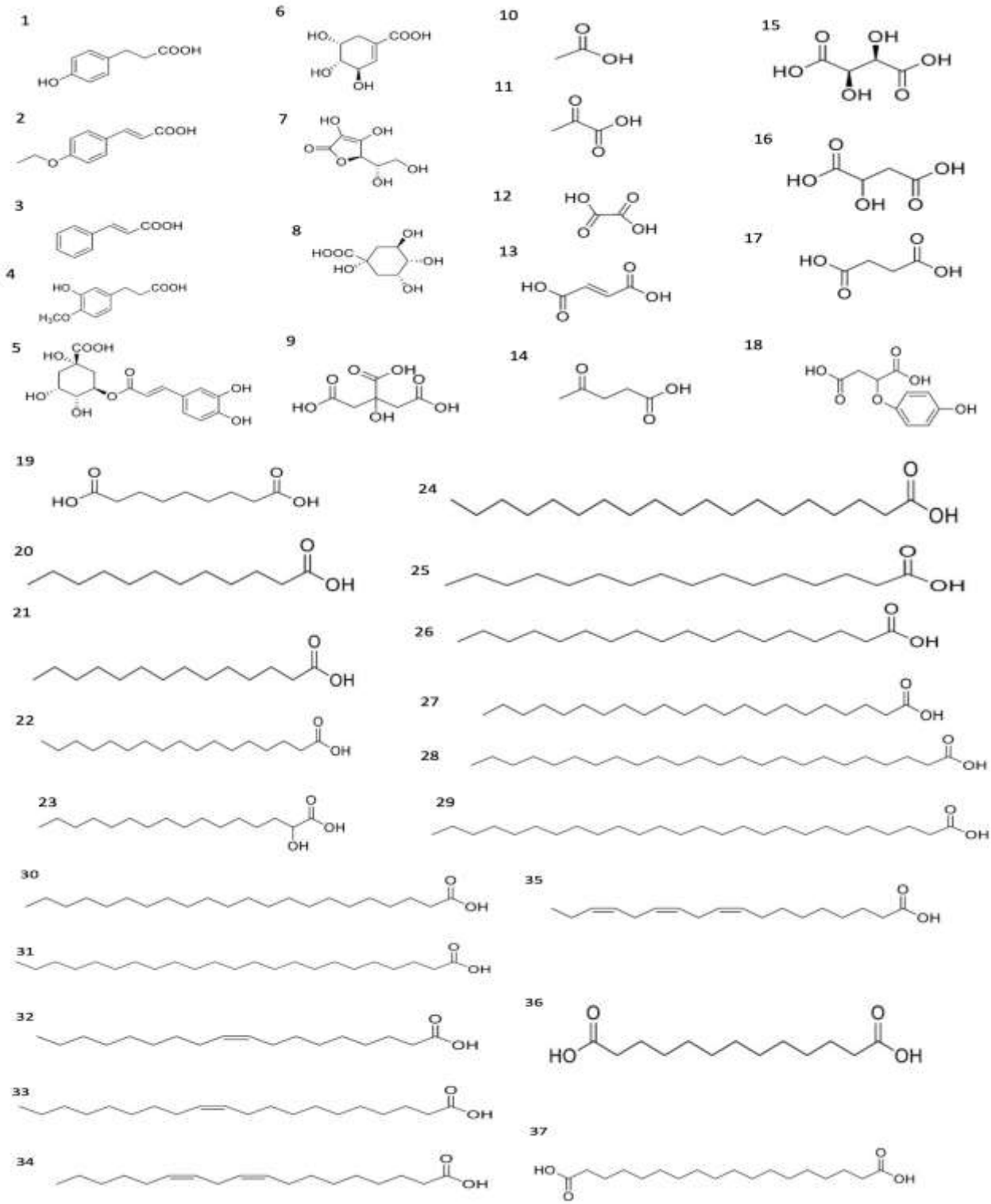

Figure 4: Structures of fatty acids and organic acids isolated from hawthorn: (1) 3-(4-Hydroxyphenyl)propionic acid; (2) trans-p-Ethoxycinnamic acid; (3) Cinnamic acid; (4) 3-(4-Methoxyphenyl)propionic acid; (5) Chlorogenic acid; (6) Shikimic acid; (7) Ascorbic acid; (8) Quinic acid; (9) Citric acid; (10) Acetic acid; (11) Pyruvic acid; (12) Oxalic acid; (13) Fumaric acid; (14) Levulinic acid; (15) Tartaric acid; (16) Malic acid; (17) Succinic acid; (18) 2-(4-Hydroxy-2-benzyl)malic acid; (19) Nonanedioic acid; (20) Lauric acid; (21) Myristic acid; (22) Heptadecanoic acid; (23) 2-Hydroxyhexadecanoic acid; (24) Nonadecanoic acid; (25) Palmitic acid; (26) Stearic acid; (27) Heneicosanoic acid; (28) Tetracosanoic acid; (29) Cerotic acid; (30) Behenic acid; (31) Tricosanoic acid; (32) Oleic acid; (33) 11-Eicosenoic acid; (34) Linoleic acid; (35) α-Linolenic acid; (36) Tridecanedioic acid; (37) Octadecanedioic acid.

Structures of flavonoids isolated from the genus Crataegus

The health benefits of flavonoids have received increasing attention recently. Flavonoids are phenolic compounds with a C6-C3-C6 backbone structure, widely found in plants and considered important secondary metabolites. [40] Reports indicate that they exhibit various pharmacological and biochemical effects, including antiviral and antiallergic activities. Flavonoids, a large class of low molecular weight polyphenolic compounds present in fruits and vegetables, possess anti-inflammatory, antitumor, and immunomodulatory properties, in addition to their ability to regulate oxidative stress. [41]

Flavones

Among all the flavonoid classes, flavones are one of the largest. The flavone chemical structure consists of 4H-chromen-4-one with a phenyl group at position 2. Red pepper, oranges, celery, and tea all contain 7-*O*-glycosides, which constitute the majority of flavones (Figure. 5). Apigenin and luteolin are the two primary edible flavones. Apigenin is usually found in a glycosylated form, where the tricyclic core structure is linked to a sugar moiety either directly (C-glycosides) or via hydroxyl groups (O-glycosides). Members of the apigenin group include apigenin, apigenin-7-*O*-glucoside, vitexin, isovitexin, rhoifolin, and schaftoside. [42]

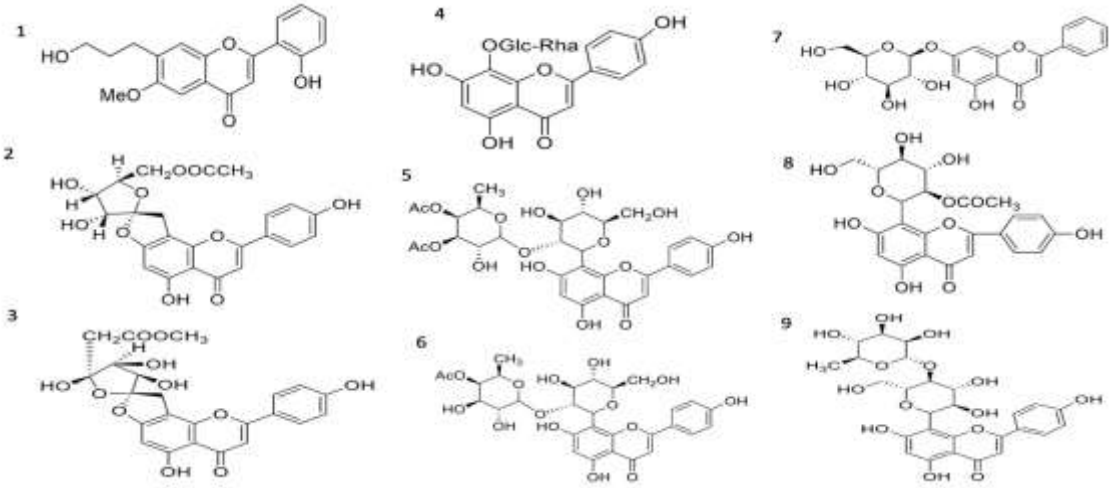

Figure 5: Flavones: (1) 2′-Hydroxy-7-(3-hydroxypropyl)-6-methoxyflavone; (2) Pinnatifinoside F; (3) Pinnatifinoside E; (4) Deacetyl-cratenacin; (5) 3‴,4‴-Di-*O*-acetyl-2″-*O*-α-rhamnosylvitexin; (6) 4‴-Acetylvitexin-2″-*O*-rhamnoside; (7) Apigenin 7-*β*-D-glucopyranoside; (8) 2″-Acetylvitexin; (9) 5,7,4′-Trihydroxyflavone 8-C-[*β*-D-glucopyranosyl (1–4)]-α-L-rhamnopyranoside.

Flavonols

The flavonol glycoside rutin exhibits a variety of pharmacological actions. [43] as a common flavonoid, rutin is believed to enhance the growth potential of human periodontal ligament stem cells (PDLSCs) and improve the regenerative capacity of periodontal tissue in inflammatory environments. Numerous studies have confirmed the positive effects of rutin on wound healing, differentiation, apoptosis, cell proliferation, as well as its anti-inflammatory, antitumor, and antioxidant properties. [44] It has also been suggested that rutin may contribute to the regeneration of periodontal tissue in an inflammatory milieu. (Figure. 6)

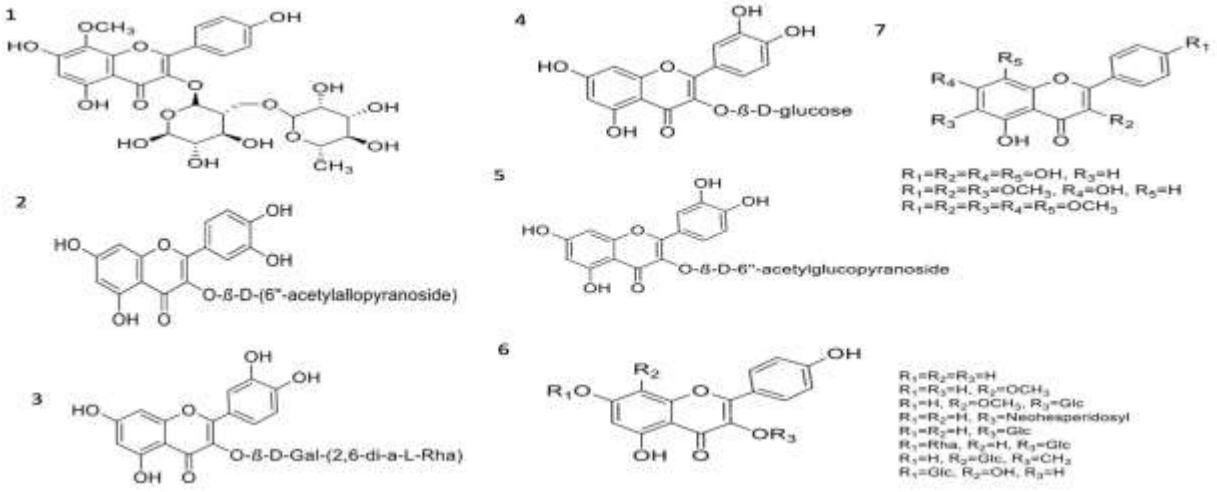

Figure 6: Flavonols: (1) 8-Methoxykaempferol 3-neohesperidoside; (2) Quercetin-3-*O*-*β*-D-6″-acetylallopyranoside; (3) Quercetin-3-*O*-(2,6-di-α-L-rhamnopyranosyl)-*β*-D-galactopyranoside; (4) Quercetin-3-*O*-*β*-D-glucopyranoside; (5) Quercetin-3-*O*-*β*-D-6″-acetylglucopyranoside; (6) Kaempferol; (7) Herbacetin.

Dihydroflavone

Regarding dihydroflavones, naringin is converted in humans to its aglycone form, naringenin, by the liver enzyme naringinase. Its water solubility is limited, and its oral bioavailability is approximately 5% (Figure. 7). The primary circulating forms of dihydroflavones in plasma are conjugates, sulfates, and glucuronides, which are rapidly metabolized following oral ingestion and absorbed into enterocytes. A significant portion is further degraded in the colon into small, absorbable phenolic compounds. Notable differences have been observed between species (e.g., human vs. rat) and between molecular forms (aglycone vs. glycoside). [45].

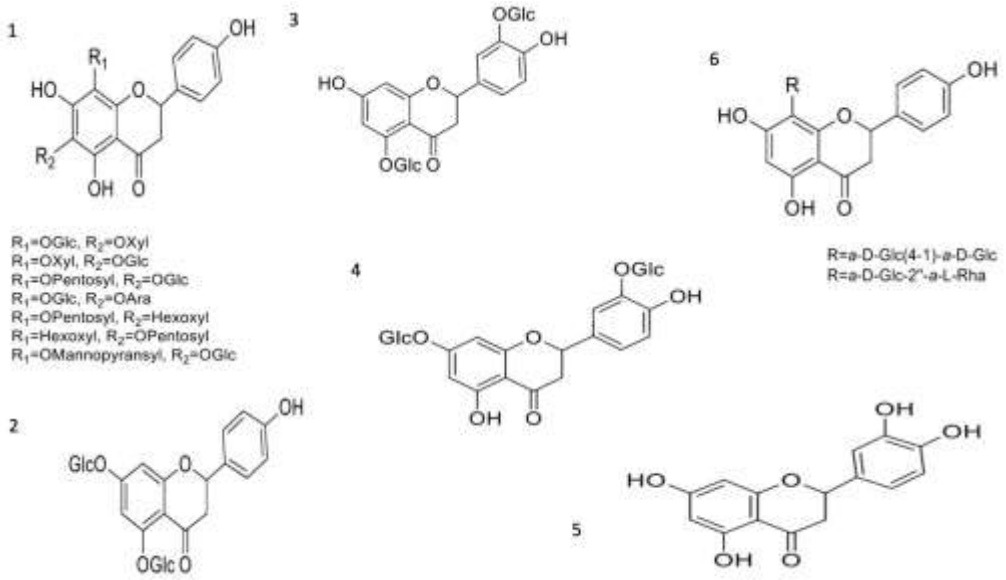

Figure: 7: Dihydroflavones: (1) Vicenin-1; (2) Naringenin-5,7-*O*-diglucoside; (3) Eriodictyol-5,3′-diglucoside; (4) Eriodictyol-7,3′-diglucoside; (5) Eriodictyol; (6) 4″-*O*-Glucosylvitexin.

Flavanols and flavanes extracted from hawthorn

One characteristic of flavanols, often referred to as flavan-3-ols, is the hydroxyl group attached to position 3 of the C ring. Unlike many other flavonoids, they lack a double bond between positions 2 and 3 (Figure 8). The hydroxylation patterns on the A, B, and C rings vary among different flavanols. Flavanols exist as monomers and are found in many fruits, serving as the building blocks for proanthocyanidin oligomers and polymers. [42]

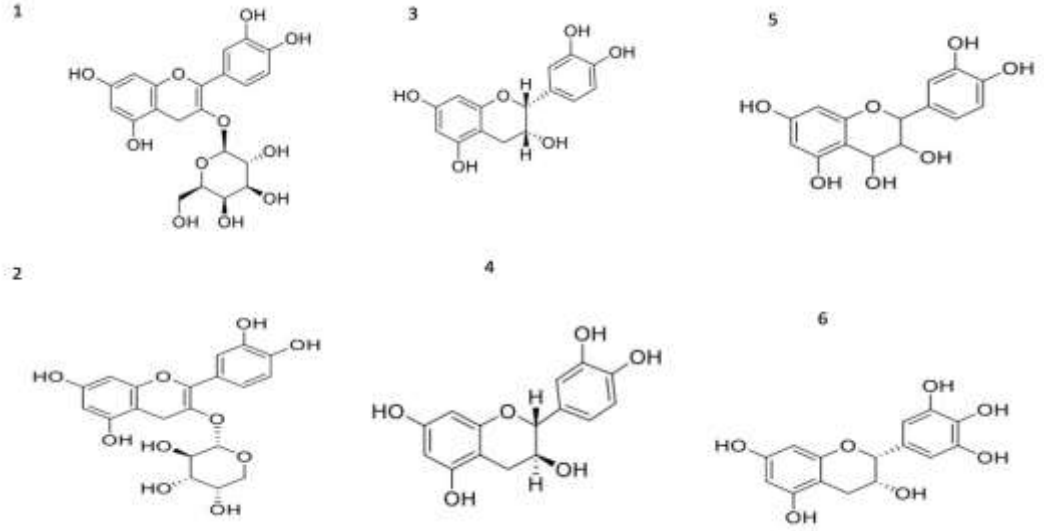

Figure: 8: Flavanes and flavanols isolated from hawthorn: (1) Cyanidin-3-*O*-*β*-galactoside; (2) Cyanidin-3-*O*-α-arabinoside; (3) (–)-Epicatechin; (4) (+)-Catechin; (5) Leucocyanidin; (6) (–)-Epigallocatechin.

Biflavonoid isolated from hawthorn

Many physiologically active flavonoid compounds, including anthocyanidins and proanthocyanidins (polymers of anthocyanidins, sometimes called biflavans or procyanidins), are found in hawthorn leaves, berries, and blossoms. [46] (Figure 9)

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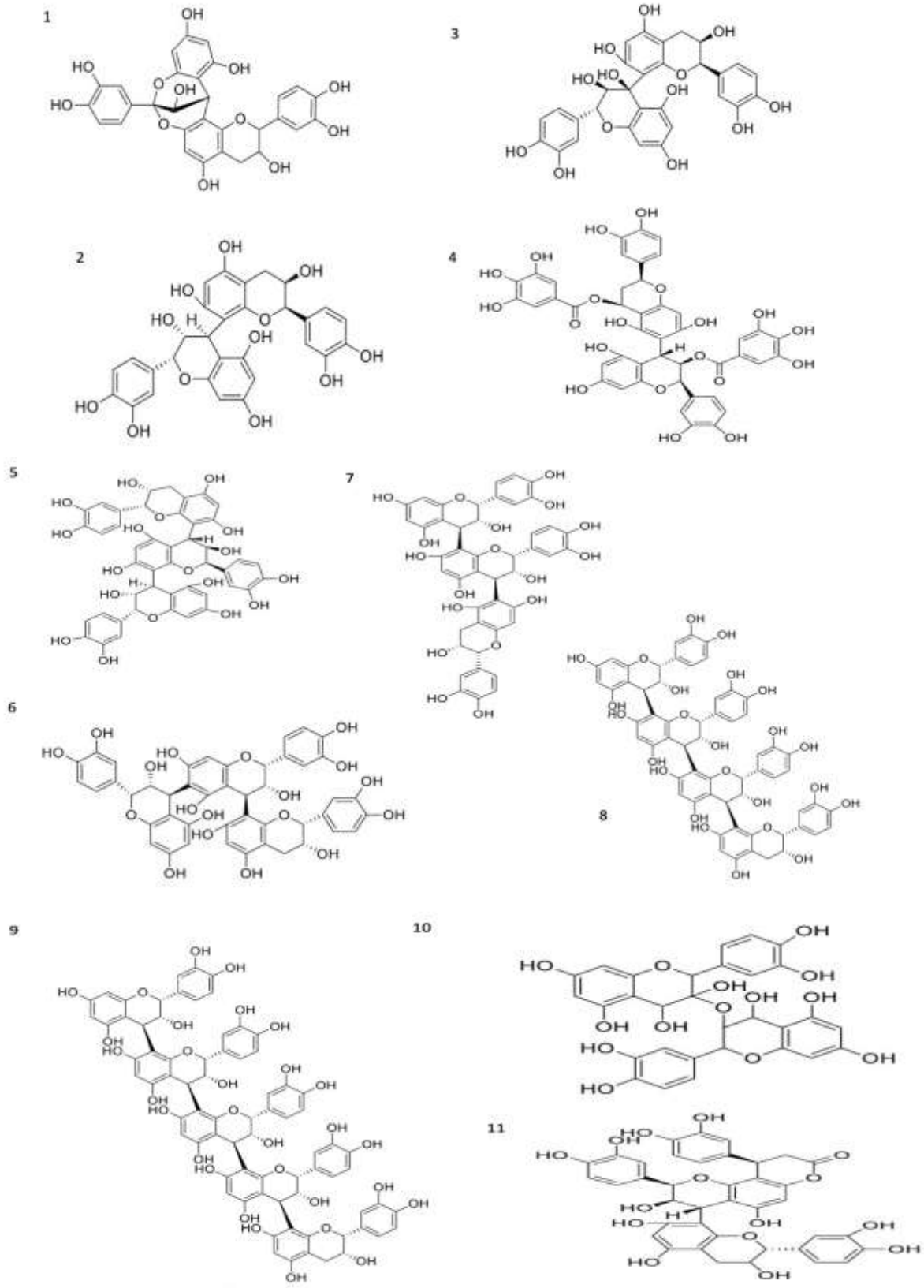


Figure 9: Biflavonoids: (1) Procyanidin A-2; (2) Procyanidin B-2; (3) Procyanidin B-4; (4) Procyanidin B-5; (5) Procyanidin C-1; (6) Epicatechin-(4β→6)-epicatechin-(4β→8)-epicatechin; (7) Epicatechin-(4β→8)-epicatechin-(4β→6)-epicatechin; (8) Procyanidin D-1; (9) Procyanidin E-1; (10) Dimeric leucocyanidin; (11) Kandelin A-1.

Anthocyanins and dihydroflavonols extracted from hawthorn

Figure 10 represents dihydroflavonols and anthocyanins. Anthocyanins, also known as anthocyanidins, are a class of naturally occurring water-soluble pigments that provide plants with a variety of colors, such as purple, lilac, red, pink, and blue, with the intensity of coloration varying according to pigment concentration. The purple color of eggplant peel is mainly caused by anthocyanins. As anthocyanin accumulation continues, the peel's color shifts from fuchsia to a deeper blackish purple. Anthocyanins are produced via the phenylpropanoid and flavonoid biosynthesis pathways. The anthocyanin synthesis pathway is one of the most important branches of flavonoid biosynthesis. This complex set of enzymatic activities involves three main stages: forming the basic anthocyanin skeleton, generating anthocyanin precursors, and converting these precursors into various anthocyanin glycosides. During anthocyanin production, phenylalanine ammonia-lyase (PAL), cinnamate 4-hydroxylase (C4H), and 4-coumarate-CoA ligase (4CL) initially transform phenylalanine into 4-coumaroyl-CoA. Subsequently, chalcone synthase (CHS), chalcone isomerase (CHI), and flavanone 3-hydroxylase (F3H) convert 4-coumaroyl-CoA into dihydroflavonol. Then, dihydroflavonol undergoes three branches of conversion into various anthocyanidins via anthocyanidin synthase (ANS), dihydroflavonol 4-reductase (DFR), flavonoid 3′-hydroxylase (F3′H), and flavonoid 3′,5′-hydroxylase (F3′5′H). The types of anthocyanin synthesis and branching are determined by F3′H and F3′5′H.[47]

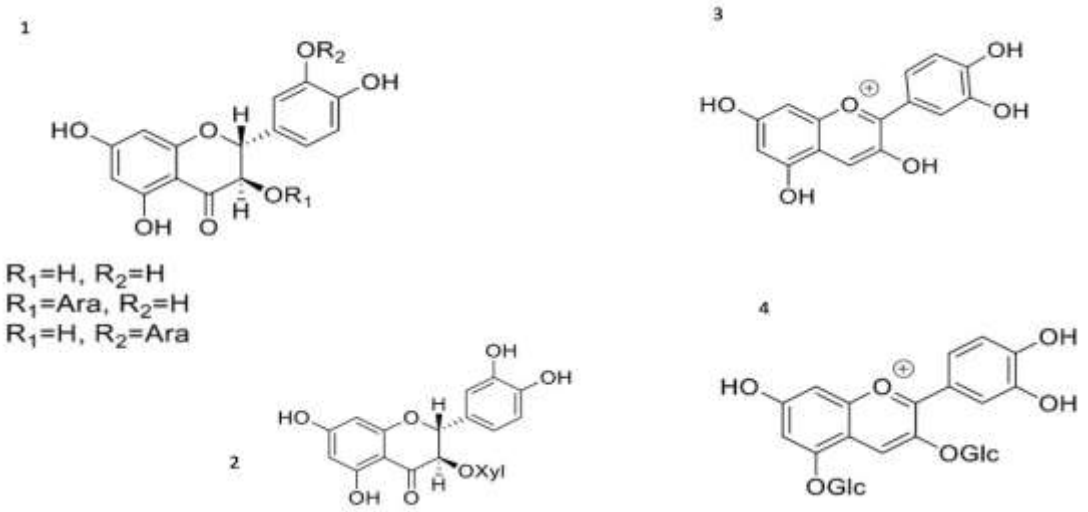
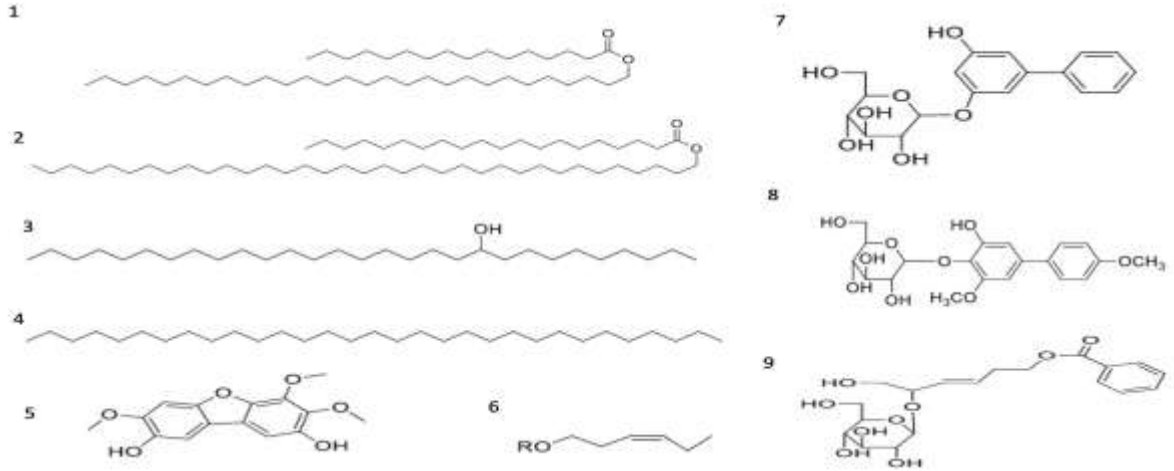


Figure 10: Dihydroflavonols and anthocyanins: (1) (+)-Taxifolin; (2) (+)-Taxifolin 3-*O*-xylopyranoside; (3) Cyanidin; (4) Pelargonin.

Other chemicals that were separated from hawthorn and their structures

Alongside active ingredients, alkanes and alkaloids (Figure 11), mostly derived from plants, are a class of naturally occurring organic compounds that contain nitrogen atoms in their molecular structures, usually as part of heterocyclic rings. They exhibit a wide range of molecular structures, including pyrrolidine, isoquinoline, and indole cores, illustrating their remarkable chemical diversity. Their structural variety underlies their broad spectrum of pharmacological effects, making them essential in the development of new therapeutics. [48] (Figure 11).



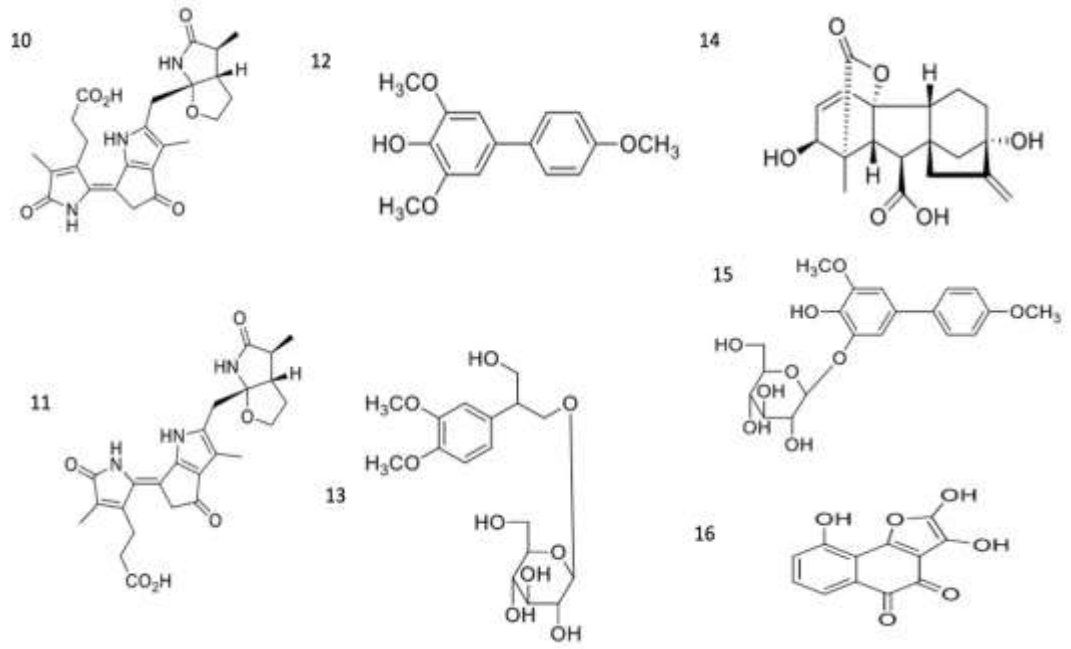


Figure: 11 Alkanes and alkaloids: (1) Hexadecanoic acid, octaconsyl ester; (2) Eicosanoic acid, octatriacontyl ester; (3) Nonacosan-10-ol; (4) Hentriacontane; (5) 2,8-Dihydroxy-3,4,7-trimethoxydibenzofuran; (6) (Z)-3-Hexenyl-*O*-*β*-D-glucopyranosyl-(1″→6′)-*β*-D-glucopyranoside; (7) Shanyenoside F; (8) Shanyenoside G; (9) Shanyenoside H; (10) Cp-TCC-1; (11) Cp-TCC-2; (12) 3,5,4′-Trimethoxy-4-hydroxybiphenyl; (13) 2-(3′,4′-Dimethoxyphenyl)-1,3-propanediol-1-*O*-*β*-D-glucopyranoside; (14) Gibberellic acid; (15) Shanyenoside A; (16) Crataequinone B

Impact of pharmacology

Reports of triterpenoids, phenolics, and flavones, which can function as taxonomic markers, dominate the comprehensive chemistry of the Rosaceae family. The Rosaceae family comprises approximately 124 genera and four subfamilies. Moreover, phylogenetic and morphological studies have revealed that the 3,300 species within the genus *Crataegus* are polyphyletic. The morphological diversity observed in most genera may cause difficulties in species identification. To enhance our understanding of the relationships among these taxa, further investigation is required. Triterpenoids are characteristic compounds of the Rosaceae family. [49] Additionally, the quantity and selectivity of extract components are influenced by the extraction method and solvent used. Most phenolic compounds and other phytochemicals containing hydroxyl groups dissolve well in polar solvents such as hydroethanolic solutions. [50] Among these compounds are flavonoids (including flavonols, flavones, flavanols, flavanones, isoflavones, anthocyanins, and proanthocyanidins), phenolic acids (hydroxybenzoic acids and hydroxycinnamic acids), vitamins, and carotenoids. These bioactive compounds can delay or prevent lipid and molecular oxidation by inhibiting the initiation or propagation of oxidative chain reactions. [51] Studies have shown that the effects of hawthorn fruit ethanol extracts are greater than those of methanol extracts. Furthermore, hawthorn fruit extracts inhibit cell growth and proliferation in optical density (OD) assays, with activities increasing proportionally to concentration. [52] Fruit coloration results from oligomeric proanthocyanidins (OP), which are predominant in leaves, fruits, and flowers. An interesting study reported that OP in hawthorn extracts reduces oxidative stress in the heart after reperfusion injury and appears to prevent apoptosis. [53]

Oligomeric procyanidins were found to reduce blood pressure while increasing heart rate, contractility, and blood flow. Additionally, a combination of triterpene acids from a commercial *Crataegus* extract was shown to enhance blood flow. [54] Fruit acids that promote blood circulation and facilitate nutrient digestion are considered quality characteristics of hawthorn fruit. [55] Methanolic extracts containing coumarins, tannins, anthraquinones, terpenoids, saponins, and phlobatannins have been reported. These phytochemicals are known for various pharmacological and biochemical effects when consumed by animals, exhibiting either cytotoxic or cell-protective activities. Similar phytochemical profiles were observed in *Crataegus* species, specifically *C. laevigata* and *C. monogyna*. [56]Recent studies indicate that the leaves, fruits, and flowers of *Crataegus* contain a wide variety of chemical constituents, including sugars and sugar alcohols, organic and phenolic acids, terpenes, and essential oils (comprising terpenoids and phenylpropanoid derivatives). [11] Our results suggest that 50% ethanol extracts from *C. pinnatifida* have potential as useful ingredients with antidiabetic and antioxidant effects. [57] Numerous studies investigating the possible mechanisms of *C. aronia*'s hypolipidemic action demonstrated that the plant may inhibit intestinal acyl-CoA cholesterol acyltransferase activity, thereby reducing triglyceride synthesis by *C. aronia* flavonoids and suppressing lipogenesis in rat liver. Previous research showed that administering *C. aronia* significantly increased the antioxidant potential of aortic cells by lowering malondialdehyde (MDA) levels and increasing glutathione (GSH) and superoxide dismutase (SOD) activity. [58] Our findings revealed that *Crataegus* (at doses of 100 and 300 mg) reduced blood glucose levels in diabetic rats. [59] Earlier α-glucosidase inhibition studies demonstrated that polyphenols, mainly composed of epicatechin and procyanidin B2, exhibit heterogeneous inhibitory kinetics with noncompetitive inhibition patterns.[60] Previous research also showed that hawthorn leaf flavonoids (HLF) can enhance antioxidant capacity and prevent lipid peroxidation in diabetic rats when administered orally at 200 mg/kg for 12 weeks.[61] Oral administration of *Crataegus* extracts at doses of 100, 300, and 1000 mg/kg for two weeks reduced the time spent in the dark compartment in diabetic rat models and improved passive avoidance learning (PAL).[61] Unripe hawthorn fruit juices have been used for muscle relief, arthritis, and some skin conditions, in addition to cosmetic applications. Dried fruits

exhibit diuretic effects. [62] A recent investigation into the antidiabetic potential of *C. pinnatifida* fruit involved drying and grinding the fruit, followed by extraction using solvents such as methanol (MeOH) and ethyl acetate (EtOAc). The resulting extracts exhibited inhibitory activity against α-glucosidase *in vitro*. Among them, the EtOAc fraction showed the strongest α-glucosidase inhibition, with an IC_{50} value of 22.70 µg/ml, outperforming the positive control acarbose, which had an IC_{50} of 81.65 µg/ml. The MeOH extract and various other fractions from *C. pinnatifida* also demonstrated α-glucosidase inhibitory effects. Column chromatography identified bioactive constituents including triterpenic acids (ursolic acid, oleanolic acid, and 3-epicorosolic acid), hyperoside, and chlorogenic acid in the extracts. Chlorogenic acid and hyperoside were isolated specifically from the EtOAc fraction, confirming their α-glucosidase inhibitory activities. Potent α-glucosidase inhibitors ursolic acid and oleanolic acid were found in the CH_2Cl_2 fraction. Each compound also inhibited protein-tyrosine phosphatase 1B (PTP1B), an enzyme vital for insulin regulation. Notably, 3-epicorosolic acid acted as a mixed-type inhibitor of PTP1B and an uncompetitive inhibitor of α-glucosidase. [63] Another study reported that the alcoholic extract of *Crataegus oxyacantha* (AEC) protected against mitochondrial lipid peroxidation, preserved Krebs cycle enzyme activities impaired by isoproterenol in rat hearts, and maintained mitochondrial antioxidant defenses. [64] the methanolic extract of *C. monogyna* from Spain contained compounds such as apigenin, isovanillic acid, kaempferol, quercitrin, and ursolic acid. Additionally, flavonoids including arbutin, rutin, hesperetin, kaempferol, and quercitrin were detected. These variations depend on the type of extract and analytical methods used. [65] The authors suggested involvement of the cyclic guanosine monophosphate (cGMP) pathway and highlighted the role of procyanidins in activating tetraethylammonium-sensitive K^+ channels in endothelial cells. This activation likely leads to endothelial membrane hyperpolarization and subsequent Ca^{2+} influx, which then stimulates endothelial nitric oxide synthase (eNOS). [66] Regarding the connection between the phenolic profile of *C. monogyna* extracts and their vasorelaxant effects, several identified compounds have previously demonstrated vasorelaxant activity. Chlorogenic acid and rutin induce endothelium-dependent vasorelaxation through nitric oxide (NO) and prostaglandin-mediated mechanisms in aortic rings; rutin also activates ATP-sensitive K^+ channels. [66] Recent research revealed that ethyl vanillin (EVA) has significantly stronger antioxidant activity than vanillin in oxidative hemolysis inhibition assays. EVA also reduced elevated reactive oxygen species (ROS) levels and metalloproteinase-9 expression in LPS-stimulated macrophage cells, suggesting potential neuroprotective effects against oxidative damage. [67] Previous studies evaluated the anti-inflammatory effects of *C. monogyna* components such as procyanidins and triterpenes. Procyanidins, particularly procyanidin B2, inhibit cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), key enzymes in the inflammatory process. In vitro experiments demonstrated significant inhibition of COX-2 protein production by procyanidins from *C. monogyna* fruit. [65]

Conclusion

The current review has demonstrated that hawthorn contains a variety of bioactive natural compounds, including triterpenes and flavonoids, which confer a broad spectrum of pharmacological benefits. Hawthorn is particularly valuable in the prevention and/or treatment of cardiovascular diseases. Indeed, it exerts beneficial effects on cardiac function and can reduce cardiovascular risk factors such as thrombosis and hypertension. Given its multiple health-promoting properties, hawthorn is a promising candidate for future clinical trials aimed at further exploring its therapeutic potential. Moreover, future research on hawthorn should focus on identifying the bioactive constituents primarily responsible for its pharmacological effects and enhancing their production through biotechnological methods, as well as elucidating the precise molecular mechanisms underlying its pharmacological activities.

Conflict of Interest

The authors declare no conflicts of interest.

Author's Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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