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# Chemical and Biological Potential of *Ammi visnaga* (L.) Lam. and *Apium graveolens* L.: A Review (1963-2020)

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**Abstract**

Medicinal plants have a vital role in our life, providing us with a variety of secondary metabolites with varied chemical structures and biological activities. *Ammi visnaga* (L.) Lam. and *Apium graveolens* L. are common traditional plant species that have long been used for the prevention and treatment of several health problems. Both *A. visnaga* and *A. graveolens* belong to the carrot family, Apiaceae (Umbelliferae) and showed different groups of natural compounds, such as coumarins, furanochromones, flavonoids and essential oils. In view of that, the current review describes various classes of chemical constituents identified so far from these medicinal species, together with their valued pharmacological and therapeutic effects.

***Key words***

*Ammi visnaga*, *Apium graveolens*, Apiaceae (Umbelliferae), Natural products, Biological activities.

## 1. Introduction

Family Apiaceae (Umbelliferae) is a family of aromatic and flowering plants, known as celery, carrot or parsley family, or simply as umbellifers. It includes more than 3000–3750 species in 300–455 genera. Plants of this family are characterized by a heavy aromatic smell due to the presence of essential oils. The family Apiaceae consists of three subfamilies, namely Apioideae, Saniculoideae and Hydrocotyloideae; each is divided into tribes and subtribes [1-5]. The most common members of this family include *Anethum graveolens* L. (dill), *Anthriscus cerefolium* L. (chervil), *Angelica* spp. (angelica), *Apium graveolens* L. (celery), *Carum carvi* L. (caraway), *Coriandrum sativum* L. (coriander), *Cuminum cyminum* L. (cumin), *Foeniculum vulgare* Mill. (fennel) and *Pimpinella anisum* L. (anise), …etc. [2,3]. Apiaceous plants have been shown to possess different biological properties, including; antimicrobial, antitumor, hepatoprotective and apoptotic activities [2].

## 2. Results and discussion

### 2.1. *A. visnaga*

*A. visnaga* is widely distributed in North Africa, Europe, Atlantic Islands, southwestern Asia, North America and Eastern Mediterranean region [6]. The fruits of *A. visnaga* were used in the treatment of mild angina symptoms, mild obstruction of the respiratory tract in bronchial asthma, as a postoperative treatment for patients with renal calculi, for intestinal cramps, pain with menstruation and as a diuretic [6, 7].

### 2.1.1. Phytochemical review

*A. visnaga* contains several classes of secondary metabolites, noticed from the isolated groups of compounds, including furanochromones, coumarins, flavonoids and essential oil. A comprehensive list of the previously isolated compounds from *A. visnaga* is presented in Table 1 and Figure 1.

### 2.1.2. Biological review

#### 2.1.2.1 Antimicrobial effects

The antimicrobial potential of both the ethanolic and aqueous extracts of *A. visnaga* fruits were tested against eight pathogenic micro-organisms; *Candida tropicans*, *Leuconostic mesontroide*, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Staphylococcus aureus*, *Candida albicans* and *Pseudomonas aeruginosa* at different concentrations (0.05-50 mg/mL) by the hole-plate diffusion method. The ethanol extract demonstrated the highest activity against Gram-positive bacteria with a minimum inhibitory concentration (MIC) of 5 mg/mL for *E. faecalis*. In addition, the MIC value of the same extract against the Gram-negative bacteria, *E. coli* and *K. pneumonia* was 12.5 mg/mL [23].

The essential oil of *A. visnaga* fruits was also tested against *E. coli*, *E. coli* ATCC 25922, *S. aureus*, *S. aureus* ATCC 43300, *P. aeruginosa*, *P. aeruginosa* ATCC 27853, *Enterobacter aerogenes*, *K. pneumoniae* and *Morganella morganii*. The oil showed the highest activity against *E. coli*, *E. coli* ATCC 25922, *S. aureus* ATCC 43300 and *P. aeruginosa* ATCC 27853 as indicated by the inhibitory zones' diameters (29, 25, 25 and 25 mm, respectively) [18].

#### 2.1.2.2 Cardiovascular effects

*A. visnaga* seeds were reported to reduce the pain caused by the decrease in the heart blood flow due to its $\gamma$-pyrone components. Visnadin, visnagin and khellin have cardiovascular effects due to their calcium channel blocking properties [24-26].

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**Table 1**: A list of previously reported compounds from *A. visnaga*.

| No. | Name | Molecular weight | Molecular formula | Organ | Ref. |
|---|---|---|---|---|---|
| | **A) γ-Pyrones (Furanochromones)** | | | | |
| **1** | Khellinol | 246.21 | $C_{13}H_{10}O_5$ | Fruits | [8] |
| **2** | 4-Norvisnagin | 216.19 | $C_{12}H_8O_4$ | Fruits | [8] |
| **3** | Visamminol [syn.: 1''-Deoxy (*S*) angelicain] | 276.28 | $C_{15}H_{16}O_5$ | Fruits | [8] |
| **4** | Khellin | 260.24 | $C_{14}H_{12}O_5$ | Fruits | [8] |
| **5** | Visnagin | 230.22 | $C_{13}H_{10}O_4$ | Fruits | [8] |
| **6** | Ammiol | 276.24 | $C_{14}H_{12}O_6$ | Fruits | [8] |
| **7** | Khellol | 246.21 | $C_{13}H_{10}O_5$ | Fruits | [8] |
| **8** | Khellol-*O*-*β*-D-glucoside | 408.40 | $C_{19}H_{20}O_{10}$ | Seeds | [9] |
| **9** | Ammiol-*O*-*β*-D-glucoside | 438.40 | $C_{20}H_{22}O_{11}$ | Seeds | [9] |
| **10** | Pimolin | 460.43 | $C_{26}H_{20}O_8$ | Fruits | [10] |
| **11** | Cimifugin | 306.31 | $C_{16}H_{18}O_6$ | Umbels | [11] |
| **12** | Prim-*O*-*β*-D glucosyl cimifugin | 468.45 | $C_{22}H_{28}O_{11}$ | Umbels | [11] |
| | **B) Benzofurans** | | | | |
| **13** | Khellinone | 236.22 | $C_{12}H_{12}O_5$ | Fruits | [8] |
| **14** | Visnaginone | 206.19 | $C_{11}H_{10}O_4$ | Fruits | [8] |
| | **C) Pyranocoumarins** | | | | |
| **15** | Samidin | 386.40 | $C_{21}H_{22}O_7$ | Fruits | [12] |
| **16** | (9*R*,10*R*)-9-*O*-(3-Methylbutanoyl)-10-acetate khellactone [syn.: Dihydrosamidin] | 388.41 | $C_{21}H_{24}O_7$ | Fruits | [12] |
| **17** | Visnadine | 388.41 | $C_{21}H_{24}O_7$ | Fruits | [6] |
| **18** | *Z*-Khellactone-3'-*β*-D-glucopyranoside | 438.43 | $C_{21}H_{26}O_{10}$ | Fruits | [13] |
| | **D) Furanocoumarins** | | | | |
| **19** | Xanthotoxin | 216.19 | $C_{12}H_8O_4$ | Fruits | [12] |
| **20** | Bergapten | 216.19 | $C_{12}H_8O_4$ | Fruits | [12] |
| **21** | Psoralen | 186.16 | $C_{11}H_6O_3$ | Fruits | [12] |
| | **E) Flavonoids** | | | | |
| **22** | Rhamnazin | 330.29 | $C_{17}H_{14}O_7$ | Fruits | [8] |
| **23** | Isorhamnetin | 316.26 | $C_{16}H_{12}O_7$ | Fruits | [8] |
| **24** | Quercetin | 302.23 | $C_{15}H_{10}O_7$ | Aerial parts | [14] |
| **25** | Rhamnetin | 316.26 | $C_{16}H_{12}O_7$ | Aerial parts | [14] |
| **26** | Rhamnetin-3-*O*-*β*-D-glucopyranoside | 478.40 | $C_{22}H_{22}O_{12}$ | Aerial parts | [14] |
| **27** | Isorhamnetin-3-*O*-*β*-D-glucopyranoside | 478.40 | $C_{22}H_{22}O_{12}$ | Aerial parts | [14] |
| **28** | Rhamnazin-3-*O*-*β*-D-glucopyranoside | 492.43 | $C_{23}H_{24}O_{12}$ | Aerial parts | [14] |
| **29** | Isorhamnetin-7-*O*-*β*-D-glucopyranoside | 478.40 | $C_{22}H_{22}O_{12}$ | Aerial parts | [14] |
| **30** | Quercetin-3-*O*-rutinoside | 610.52 | $C_{27}H_{30}O_{16}$ | Aerial parts | [14] |
| **31** | Quercetin-3-*O*-*β*-D-glucopyranoside | 464.40 | $C_{21}H_{20}O_{12}$ | Aerial parts | [14] |
| **32** | Isorhamnetin-3-*O*-rutinoside | 624.54 | $C_{28}H_{32}O_{16}$ | Aerial parts | [14] |
| **33** | Quercetin-7,3,3'-*O*-triglucopyranoside | 788.66 | $C_{33}H_{40}O_{22}$ | Aerial parts | [14] |
| **34** | Kaempferol | 286.24 | $C_{15}H_{10}O_6$ | Fruits | [15] |
| **35** | Kaempferol-3-rutinoside | 594.52 | $C_{27}H_{30}O_{15}$ | Leaves, flowers and fruits | [16] |
| **36** | Kaempferol-3-*O*-*β*-D-glucopyranoside | 448.40 | $C_{21}H_{20}O_{11}$ | Leaves, flowers and fruits | [16] |
| **37** | Apigenin | 270.24 | $C_{15}H_{10}O_5$ | Fruits | [15] |
| **38** | Luteolin | 286.24 | $C_{15}H_{10}O_6$ | Fruits | [15] |
| **39** | Chrysoeriol | 300.26 | $C_{16}H_{12}O_6$ | Fruits | [15] |
| **40** | Quercetin-3-sulfate | 382.30 | $C_{15}H_{10}O_{10}S$ | Leaves, flowers and fruits | [16] |
| **41** | Rhamnetin-3-sulfate | 396.33 | $C_{16}H_{12}O_{10}S$ | Leaves, flowers and fruits | [16] |
| **42** | Isorhamnetin-3-sulfate | 394.31 | $C_{16}H_{10}O_{10}S^{-2}$ | Leaves, flowers and fruits | [16] |
| **43** | Genistin | 432.40 | $C_{21}H_{20}O_{10}$ | Leaves and roots | [17] |
| **44** | Sissotrin | 446.40 | $C_{22}H_{22}O_{10}$ | Leaves and roots | [17] |
| **45** | Isoformononetin | 268.26 | $C_{16}H_{12}O_4$ | Leaves and roots | [17] |
| **46** | Formononetin | 268.26 | $C_{16}H_{12}O_4$ | Leaves and roots | [17] |
| **47** | Prunetin | 284.26 | $C_{16}H_{12}O_5$ | Leaves and roots | [17] |
| **48** | Biochanin-A | 284.26 | $C_{16}H_{12}O_5$ | Leaves and roots | [17] |
| **49** | Daidzein | 254.24 | $C_{15}H_{10}O_4$ | Leaves and roots | [17] |
| **50** | 4',6,7-Trihydroxyisoflavone | 270.24 | $C_{15}H_{10}O_5$ | Leaves and roots | [17] |

| No. | Name | Molecular weight | Molecular formula | Organ | Ref. |
|---|---|---|---|---|---|
| | | **F) Essential oil** | | | |
| **51** | *α*-Thujene | 136.23 | $C_{10}H_{16}$ | Aerial parts | [18] |
| **52** | 3-Methylpentenol | 100.16 | $C_6H_{12}O$ | Aerial parts | [18] |
| **53** | *β*-Myrcene | 136.23 | $C_{10}H_{16}$ | Aerial parts | [18] |
| **54** | Isobutyl isobutyrate | 144.21 | $C_8H_{16}O_2$ | Aerial parts | [18] |
| **55** | Butyl isobutyrate | 144.21 | $C_8H_{16}O_2$ | Fruits | [19] |
| **56** | Linalool | 154.25 | $C_{10}H_{18}O$ | Aerial parts | [18] |
| **57** | 2,2-Dimethylbutanoic acid | 116.16 | $C_6H_{12}O_2$ | Aerial parts | [18] |
| **58** | *α*-Isophorone | 138.21 | $C_9H_{14}O$ | Aerial parts | [18] |
| **59** | 2-Nonyne | 124.22 | $C_9H_{16}$ | Aerial parts | [18] |
| **60** | Bornyl acetate | 196.29 | $C_{12}H_{20}O_2$ | Aerial parts | [18] |
| **61** | Thymol | 150.22 | $C_{10}H_{14}O$ | Aerial parts | [18] |
| **62** | Geranyl acetate | 196.29 | $C_{12}H_{20}O_2$ | Aerial parts | [18] |
| **63** | Lavandulyl acetate | 196.29 | $C_{12}H_{20}O_2$ | Aerial parts | [18] |
| **64** | Citronellyl propionate | 212.33 | $C_{13}H_{24}O_2$ | Aerial parts | [18] |
| **65** | Croweacin | 192.21 | $C_{11}H_{12}O_3$ | Aerial parts | [18] |
| **66** | Neryl isobutanoate | 224.34 | $C_{14}H_{24}O_2$ | Aerial parts | [18] |
| **67** | *α*-Damascone | 192.30 | $C_{13}H_{20}O$ | Aerial parts | [18] |
| **68** | (2*Z*,6*E*) Farnesal | 220.35 | $C_{15}H_{24}O$ | Aerial parts | [18] |
| **69** | Isoamyl-2-methylbutyrate | 172.26 | $C_{10}H_{20}O_2$ | Fruits | [19] |
| **70** | *α*-Pinene | 136.23 | $C_{10}H_{16}$ | Whole plant | [19] |
| **71** | *β*-Pinene | 136.23 | $C_{10}H_{16}$ | Whole plant | [19] |
| **72** | *α*-Terpinene | 136.23 | $C_{10}H_{16}$ | Whole plant | [19] |
| **73** | Limonene | 136.23 | $C_{10}H_{16}$ | Whole plant | [19] |
| **74** | 3-Hexenyl isobutanoate | 170.25 | $C_{10}H_{18}O_2$ | Fresh aerial parts | [20] |
| **75** | Nerol | 154.25 | $C_{10}H_{18}O$ | Fresh aerial parts | [21] |
| **76** | Hexanal | 100.16 | $C_6H_{12}O$ | Umbels | [19] |
| **77** | Sabinene | 136.23 | $C_{10}H_{16}$ | Umbels | [19] |
| **78** | Tetracosanoic acid | 368.64 | $C_{24}H_{48}O_2$ | Aerial parts | [22] |
| **79** | Stearic acid | 284.50 | $C_{18}H_{36}O_2$ | Aerial parts | [22] |
| **80** | Petroselinic acid | 282.50 | $C_{18}H_{34}O_2$ | Fruits | [22] |
| **81** | Arachidic acid | 312.53 | $C_{20}H_{40}O_2$ | Fruits | [22] |
| **82** | *β*-Sitosterol | 414.71 | $C_{29}H_{50}O$ | Aerial parts | [22] |
| | | **G) Coumestans** | | | |
| **83** | Coumestrol | 268.22 | $C_{15}H_8O_5$ | Leaves and roots | [17] |

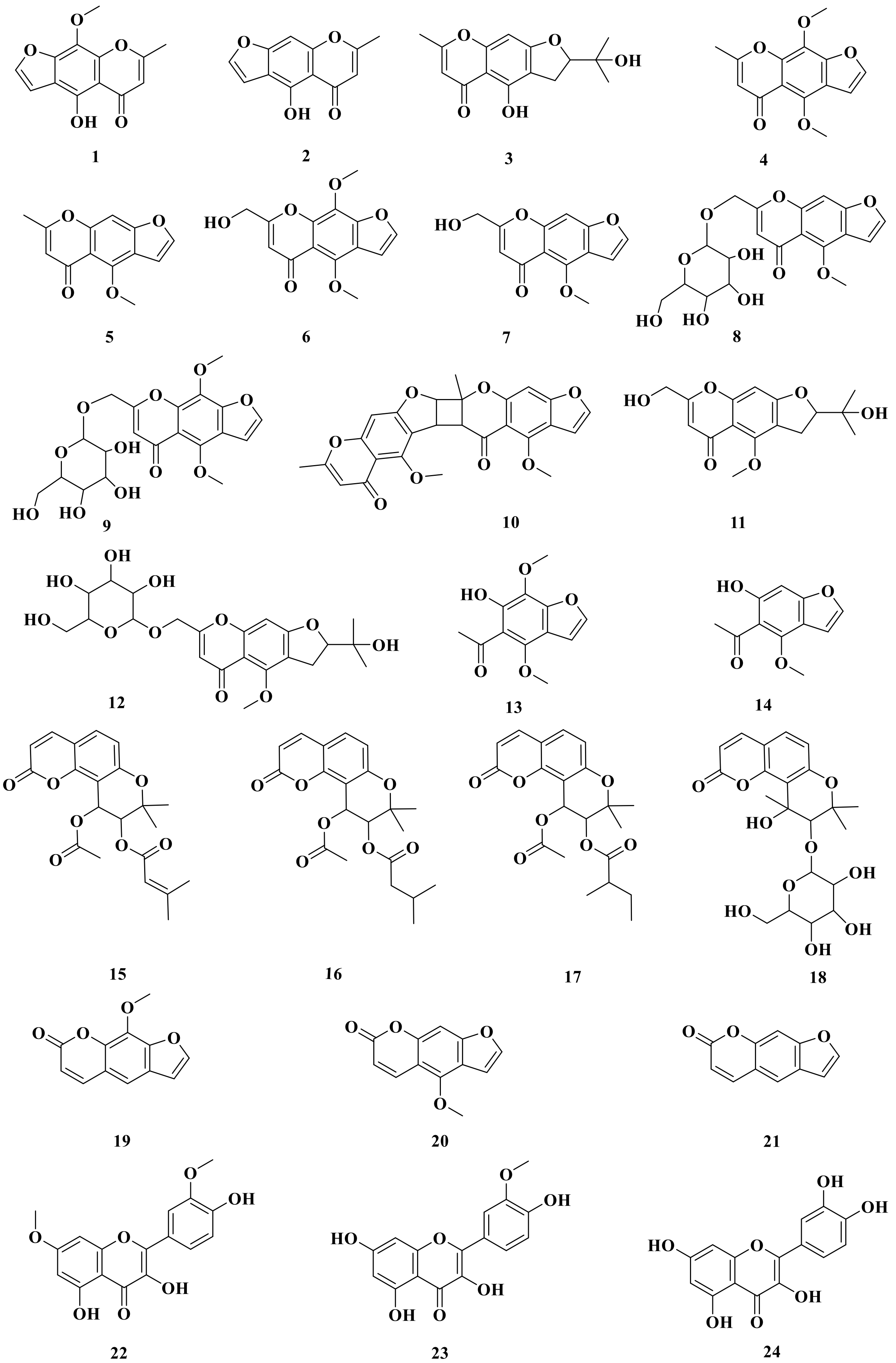
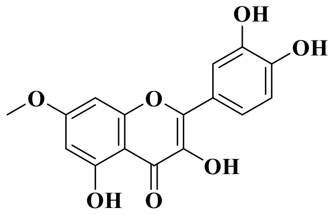



**Figure 1:** Chemical structures of the reported compounds from *A. visnaga*.



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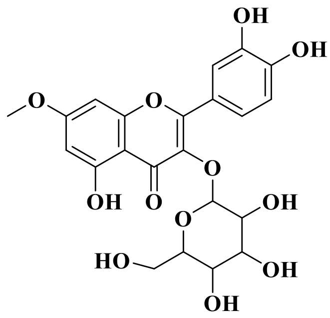

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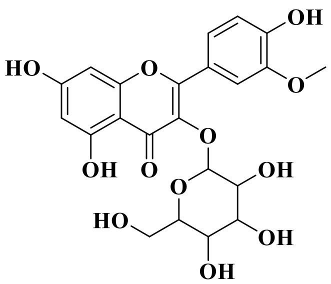

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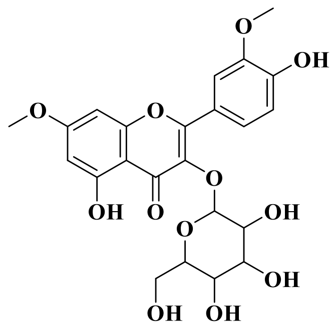

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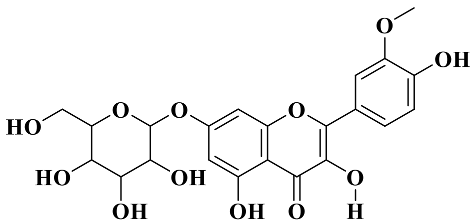

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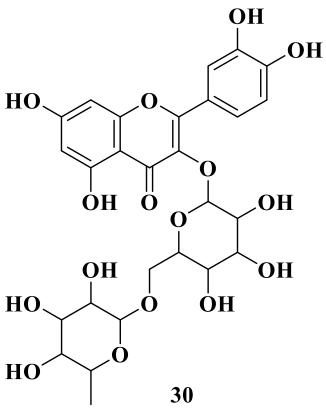

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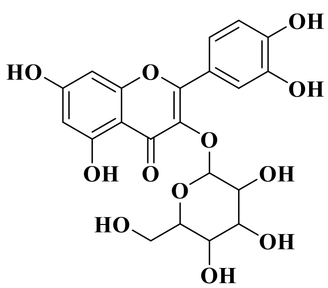

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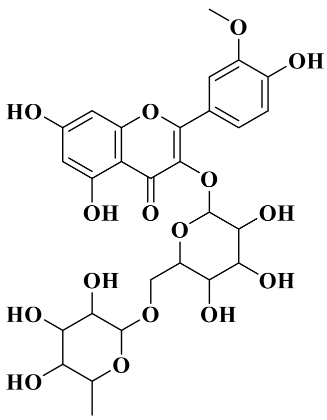

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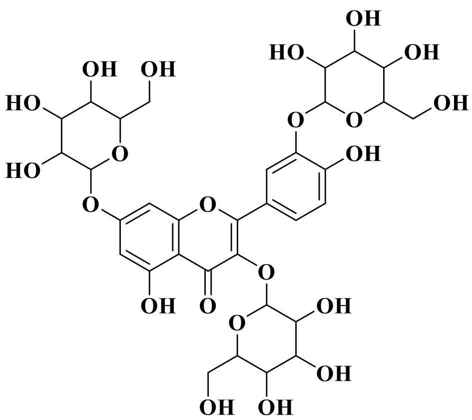

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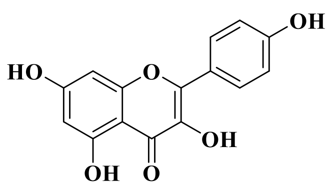

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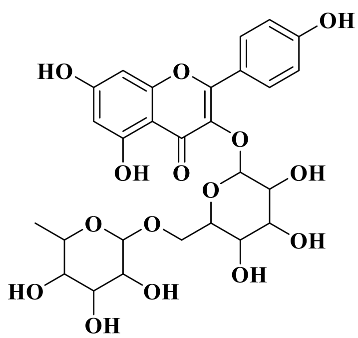

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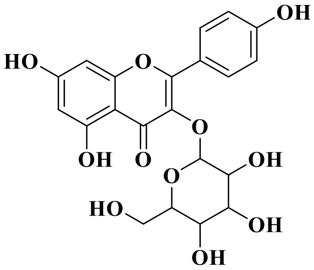
**Figure 1:** (continued).



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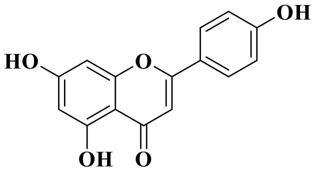

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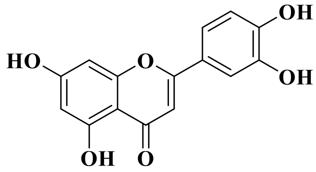

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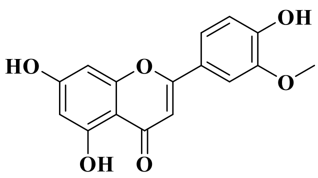

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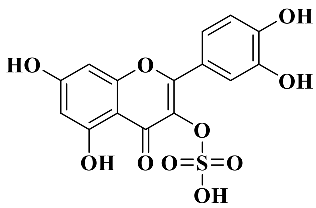

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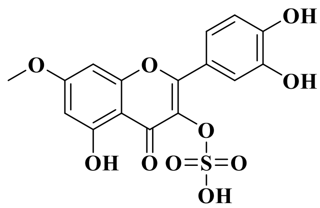

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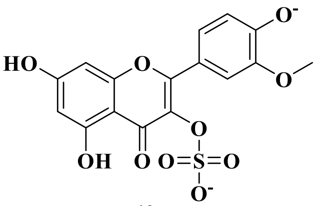

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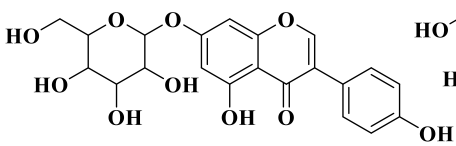

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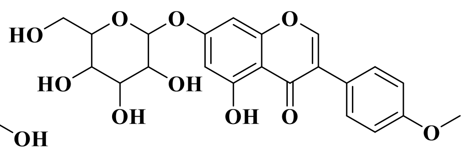

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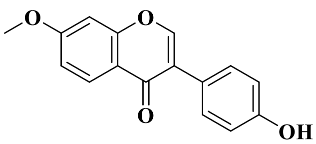

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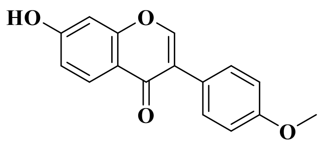

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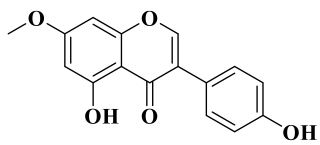

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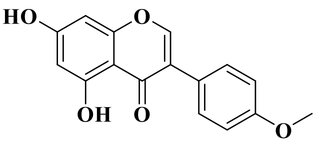

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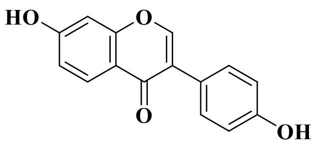

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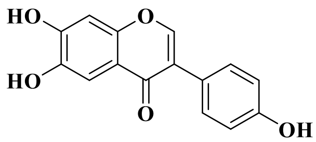

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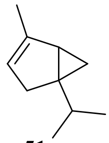
**Figure 1:** (continued).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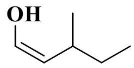
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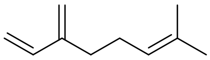
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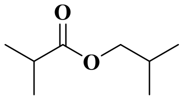
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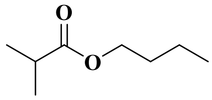
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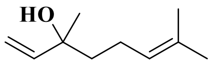
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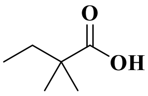
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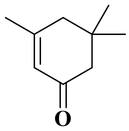
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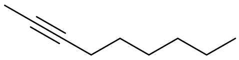
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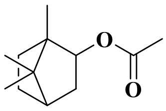
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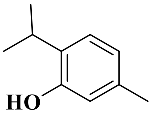
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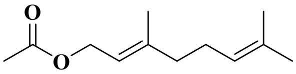
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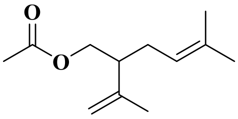
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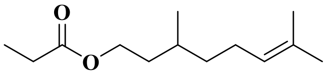
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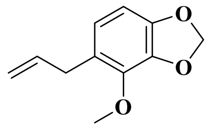
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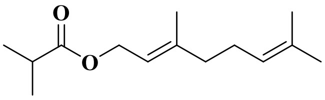
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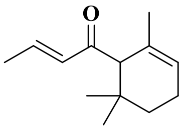
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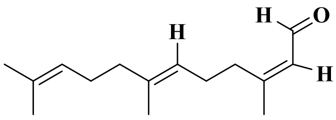
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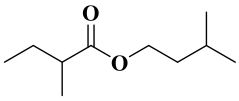
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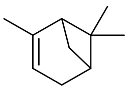
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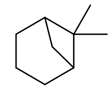
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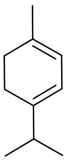
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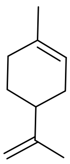
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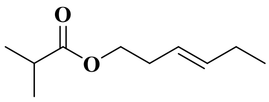
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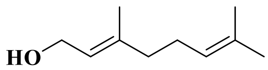
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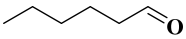
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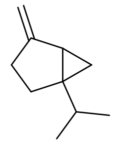
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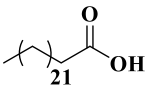
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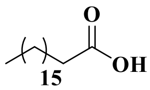
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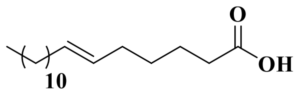
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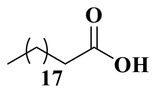
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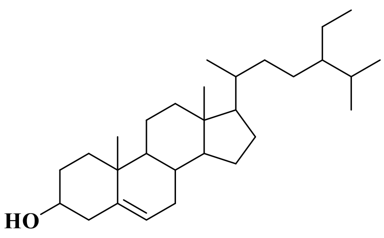
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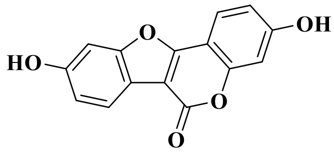
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**Figure 1:** (continued).

They inhibit the contraction of vascular smooth muscles, causing dilatation of the peripheral and coronary vessels and stimulate coronary circulation [24,25]. Both the peripheral and coronary vasodilator properties were also found with visnagin, which has been used in angina pectoris as it leads to non-specific inhibition of the contractility of vascular smooth muscles [24,25]. Moreover, it has negative inotropic and chronotropic effects and aids in reducing peripheral vascular resistance [26]. It also causes a weak inhibition of the hydrolytic activity of phosphodiesterase (PDE) isozymes (PDE5, PDE4, PDE3, cyclic GMP activated PDE2 and PDE1). This inhibitory effect on cyclic nucleotide PDEs may be responsible for the vasodilatory action of visnagin at high concentrations [26]. The chloroform and methanol extracts (at 1 mg/mL) of *A. visnaga* fruits cause the contractions of the rabbit Guinea pig aorta *in vitro* [6]. The coronary blood flow increased in isolated Guinea pig hearts via visnadin at 60 and 120 µg/mL by 46 and 57%, respectively [6]. Visnadin (< $10^{-5}$ M) was reported to cause inhibition of the contractions induced by the depolarization with 80 mM KCl or by $CaCl_2$ in the KCl-depolarized aorta. Its inhibitory effects were not increased when the depolarization time was prolonged and was similar in aorta incubated in 5 or 40 mM KCl [27]. Samidin and khellol glucoside were reported to exhibit positive inotropic effects on the heart [6]. Khellin was reported to increase HDL-cholesterol in normolipidemic subjects. It also reported having vasodilator, bronchodilator and spasmolytic activities [24]. It has been developed in the treatment of angina pectoris as a bronchodilator and coronary medicine due to its peripheral and coronary function as a vasodilator [28]. Besides being such an antiasthmatic and vasodilator and also an important relaxant without influencing blood pressure [29]. The vasodilating features of *A. visnaga* are associated with the pyranocoumarin, visnadin and its two primary pyrones, khellin and visnagin. Khellin and visnadin have been shown to have antagonistic activity with calcium, which in turn results in vasodilating activities. It has been shown that visnadin exhibits both peripheral and coronary vasodilator activities and is also used to treat angina pectoris. It inhibits the contractions mediated by the entry of Ca2 + via L-type Ca2 + channels [27].

**2.1.2.3 Prevention of kidney stone formation**

Khellin is a spasmolytic agent and visnagin also may decrease peripheral vascular resistance, which may make the stone to pass through the urinary tract easily. In an *in vitro* cell culture experimentation, khellin and visnagin exhibited preventive activity and decreased lactate dehydrogenase enzyme. Also, khellin and visnagin illustrated preventive effects *in vivo* through decreasing deposition of calcium oxalate crystals [6,30].

**2.1.2.4 Treatment of vitiligo**

Khellin has phototherapeutic activities like as those of the psoralens without the formation of detectable DNA mutations or phototoxic effects. It has therefore been used for the treatment of vitiligo [31]. A total of 36 patients suffering from different types of vitiligo underwent 6 months of treatment with a novel gel formulation of khellin (1%), based upon a water/2-propanol/propylene glycol (WPG) ternary system, caused repigmentation in 86.1% of the treated cases, as opposed to 66.6% in the placebo group [6,31].

**2.1.2.5 Antioxidant effects**

*A. visnaga* has antioxidant activity [32,33]. The antioxidant effect of the butanolic extract of *A. visnaga* was determined via the 2,2-diphenyl-1-picrylhydrazyl (DPPH) method. At a concentration of 200 µg/mL, the butanolic extract quenched the DPPH radical by 78.7% [6,34].

**2.1.2.6 Antidiabetic activities**

In many cultures, such as those of Palestine, Morocco and the Sefrou region, *A. visnaga* is considered a popular antidiabetic agent [22,35-36]. An aqueous sample containing *A. visnaga* was shown to possess a substantial hypoglycemic effect when offered to both regular and streptozotocin rats with diabetes [22,37]. In addition, a decoction formulated from the *A. visnaga* fruits had the potential in normoglycemic rats to minimize blood glucose levels by 51% in comparison to a hypoglycemic agent (tolbutamide) [22,38].

**2.1.2.7 Anti-inflammatory activities**

Visnagin decreases the expression of mRNA and the release of TNF-$\alpha$, IL-1$\beta$ and IFN$\gamma$. The anti-inflammatory activity of visnagin could be due to the inhibition of transcription factors, such as AP-1 and NF-$_{K}$B [22,39]. Visnagin also has a neuroprotective effect that is responsible for its anti-inflammatory activity [22].

**2.1.2.8 Cytotoxic activities**

The cytotoxicity of khellin was measured against four cancer cell lines: MCF-7 (breast cancer), MKN-45 (gastric cancer), HEp-2 (larynx cancer) and HT-29 (colorectal cancer). The findings were, however, not positive and the substance did not demonstrate any cytotoxic activity against the four cell lines at the tested concentrations [22,40]. Nevertheless, khellin exhibited mild to moderate activity against the hepatocellular carcinoma cell line [41]. An ethanolic extract of *A. visnaga* exhibited cytotoxic activity on cervical cancer and breast cancer cell lines [22,42]. Further research was performed into the cytotoxic activity of isolated khellin and visnagin against Hep-G2 (liver carcinoma), HCT 116 (colon carcinoma), Hela (cervical carcinoma), MCF7 (breast carcinoma) and Hep-G2 (liver carcinoma); the findings exhibited the cytotoxic activity of both khellin and visnagin against the Hep-G2 cell line [22,43].

**2.1.2.9 Hair loss**

The topical use of *A. visnaga* was tested for hair loss. A lotion consisting of visnadin and other components leading to enhancement in local microcirculatory flow [22,44].

### 2.1.2.10 Antimutagenic effects

In *Salmonella typhimurium* T98, khellin exhibited inhibitory effects of the mutagenicity of two promutagens benzo[a]pyrenes, 2-aminofluorene and 2-aminoanthracene, while visnagin illustrated a greater toxic effect. The total extract of the fruits of *A. visnaga* displayed a higher inhibition ability against 2-aminoanthracene, 1-nitropyrene and daunomycin than khellin alone. This was attributed to the presence of additional inhibitors such as coumarins or due to the synergistic effect of different compounds [22,45].

### 2.1.2.11 Immunostimulatory activities

Immunostimulatory effects were detected by *A. visnaga* total and protein extracts. Extracts were evaluated on splenocyte using an MTT (3-(4,5-dimethylthiazol-2yl)-2,5-diphenyltetrazolium bromide) assay with or without concanavalin-A (Con-A) stimulation, a mitogenic agent used as a positive control agent [46].

### 2.1.2.12 Larvicidal and insecticidal activities

Both larvicidal and insecticidal features of *A. visnaga* have been investigated and the khellin toxicity was examined against *Oncopeltus fasciatus* (Hemiptera) and *Aedes aegypti* (Diptera) larvae, where high activity was observed [22,48]. Khellin and visnagin may therefore be used for the production of new botanical acaricides [49]. *A. visnaga* fruit ethanolic extract caused inhibition of the lipid content in the haemolymph of nymphs and adults [50], while *A. visnaga n*-butanolic extract caused inhibition to glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) activity in the haemolymph [51].

### 2.1.2.13 Herbicidal activities

*A. visnaga* dichloromethane extract exhibited herbicidal activity. Khellin and visnagin were responsible for their herbicidal effect [22,52].

## 2.2 *A. graveolens*

*A. graveolens* (Apiaceae) is widely distributed in Italy, Sweden, Egypt, Algeria and Ethiopia [53]. It consists of three varieties that are classified according to the part of the plant consumed [54]; *A. graveolens* var. *dulce*; commonly known as celery, *A. graveolens* var. *rapaceum*; commonly known as celeriac or root celery and *A. graveolens* var. *secalinum*; commonly known as smallage or leaf celery. Celery is an important source of minerals, vitamins and amino acids. It has many different uses such as sedative, stimulant, carminative, laxative, antispasmodic, anthelmintic, diuretic, urinary antiseptic, emmenagogue and aphrodisiac [53,55].

### 2.2.1 Phytochemical review

*A. graveolens* contained various classes of secondary metabolites, noticed from the isolated groups of compounds including; flavonoids, coumarins, furanocoumarins, isobenzofurans, sesquiterpenes, phthalides and miscellaneous [55]. A comprehensive list of the previously isolated compounds from *A. graveolens* is presented in (Table 2 and Figure 2).

### 2.2.2 Biological review

#### 2.2.2.1 Anticancer activities

Celery seed oil (CSO) is a source of anticancer phytochemicals. When, CSO (300 mg/kg, p.o.) was given to rats for four weeks after DENA-induced hepatocellular carcinoma (diethyl nitrosamine) (HCC), its increased caspase-3 expression and decreased PCNA expression, suggesting both apoptotic and anti-proliferative activity, respectively. CSO uses anti-proliferative, anti-inflammatory and proapoptotic pathways to exert its anticancer effect [53].

#### 2.2.2.2 Antibacterial activities

The essential oil of celery displayed strong inhibitory activities against *E. coli* and moderate inhibition against *S. aureus* and *P. aeruginosa* [77].

#### 2.2.2.3 Antiulcerogenic activities

Evaluation of the antiulcerogenic activity in rats was done by using the HCl/EtOH method. Inhibition of gastric lesions by extracts of *A. graveolens* was dose-dependent for both seeds and aerial parts by (51–95%) and (53–76%), respectively. The methanolic and aqueous extracts at 300 mg/kg caused inhibition of gastric lesions, which was similar to that induced by omeprazole (94%) [77].

#### 2.2.2.4 Hypolipidemic effects

Ethanol seed extract of *A. graveolens* showed a decrease of serum total cholesterol, low-density lipoprotein cholesterol, triglycerides and significant increase in high-density lipoprotein cholesterol in the treated groups. The oral administration of ethanol seed extract of *A. graveolens* showed good hypolipidemic effects. The results agreed to the traditional use of *A. graveolens* in the treatment of hyperlipidemia [78].

#### 2.2.2.5. Antihypertensive effects

Administration of the methanolic, hexanoic and aqueous-ethanolic celery seeds extracts was used to demonstrate their effects on blood pressure and heart rate using spironolactone as a guide. The findings showed that in hypertensive rats, they decreased blood pressure and increased heart rate, but they had no effect on normotensive rats. At 300 mg/kg, each celery seed extract resulted in a decrease in blood pressure of 38, 24 and 23 mmHg and an increase in heart rate of 60, 25 and 27 beats/min, respectively [79].

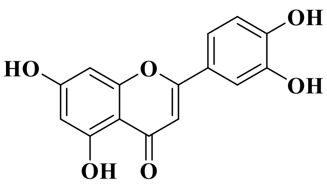
## 3. Conclusion

Several classes of secondary metabolites isolated from different parts of *A. visnaga* including furanochromones, furanocoumarins, pyranocoumarins, flavonoids and essential oil, where flavonoids and essential oil are the most common investigated classes, while others need more attention from the researchers. Fruits and aerial parts were investigated. Therefore, other parts need further investigation.

**Table 2**: A list of previously isolated compounds from *A. graveolens*.

| No. | Name | Molecular weight | Molecular formula | Organ | Ref. |
|---|---|---|---|---|---|
| | **A) Flavonoids** | | | | |
| **1** | Luteolin | 286.24 | $C_{15}H_{10}O_6$ | Leaves | [56, 57] |
| **2** | Kaempferol | 286.24 | $C_{15}H_{10}O_6$ | Leaves | [57] |
| **3** | Apiin | 564.50 | $C_{26}H_{28}O_{14}$ | Leaves | [58] |
| **4** | Luteolin-7-*O*-*β*-D-apiofuranosyl-(1→2)-*β*-D-glucopyranoside | 580.49 | $C_{26}H_{28}O_{15}$ | Leaves | [59] |
| **5** | Luteolin-7-*O*-*β*-D-glucopyranoside | 448.38 | $C_{21}H_{20}O_{11}$ | Leaves | [59] |
| **6** | Luteolin-7-*O*-[*β*-D-apiofuranosyl (1→2) -(6''-*O*-malonyl)]-*β*-D-glucopyranoside | 666.54 | $C_{29}H_{30}O_{18}$ | Leaves | [59] |
| **7** | Chrysoeriol-7-*O*-*β*-D-apiofuranosyl (1→2)-*β*-D-glucopyranoside | 594.52 | $C_{27}H_{30}O_{15}$ | Leaves | [59] |
| **8** | Apigenin-7-*O*-*β*-D-glucopyranoside [syn.: Apigetrin] | 432.40 | $C_{21}H_{20}O_{10}$ | Leaves | [60] |
| **9** | Apigenin-7-*O*-*β*-D-apiofuranosyl-(1→2)-*β*-D-glucopyranoside | 564.49 | $C_{26}H_{28}O_{14}$ | Leaves | [59] |
| **10** | Apigenin-7-*O*-[*β*-D-apiofuranosyl (1→2)-(6''-*O*-malonyl)]-*β*-D-glucopyranoside | 650.54 | $C_{29}H_{30}O_{17}$ | Leaves | [59] |
| | **B) Coumarins and furocoumarins** | | | | |
| **11** | Apiumetin | 244.24 | $C_{14}H_{12}O_4$ | Seeds | [61] |
| **12** | Apiumetin-*O*-*β*-D-glucopyranoside | 406.38 | $C_{20}H_{22}O_9$ | Seeds | [61] |
| **13** | Bergapten | 216.19 | $C_{12}H_8O_4$ | Seeds | [61] |
| **14** | Isopimpinellin | 246.21 | $C_{13}H_{10}O_5$ | Seeds | [61] |
| **15** | 8-Hydroxy-5-methoxypsoralene | 232.19 | $C_{12}H_8O_5$ | Seeds | [61] |
| **16** | 5-Methoxy-8-O-*β*-D-glucosyloxypsoralene | 394.33 | $C_{18}H_{18}O_{10}$ | Seeds | [61] |
| **17** | Isorutarin | 424.4 | $C_{20}H_{24}O_{10}$ | Seeds | [61] |
| **18** | Vellein | 392.40 | $C_{20}H_{24}O_8$ | Seeds | [61] |
| **19** | Celerin | 260.28 | $C_{15}H_{16}O_4$ | Seeds | [62] |
| **20** | 4,9-Dihydroxy-7*H*-furo[3,2-*g*][1] benzopyran-7-one-4-methylether-9-*O*-*β*-D-glucopyranoside | 394.33 | $C_{18}H_{18}O_{10}$ | Seeds | [63] |
| **21** | 7,8-Dihydroxy-6-(3-methyl-2-butenyl)-2*H*-1-benzopyran-2-one-8-methy ether | 260.29 | $C_{15}H_{16}O_4$ | Seeds | [64] |
| **22** | (1'*S*,2*S*) 2-(1,2-Dihydroxy-1-methylethyl)-2,3-dihydro-7*H*-furo[3,2*g*][1] benzopyran-7-one | 262.26 | $C_{14}H_{14}O_5$ | Seeds | [64] |
| **23** | Osthenol | 230.26 | $C_{14}H_{14}O_3$ | Seeds | [61] |
| **24** | Celereoin | 262.26 | $C_{14}H_{14}O_5$ | Seeds | [61] |
| | **C) Isobenzofurans** | | | | |
| **25** | 3-Butylhexahydro-1(3*H*)-isobenzofuranone | 196.29 | $C_{12}H_{20}O_2$ | Leaves and stalks | [65] |
| **26** | (3*R*,3*aR*,7*aS*) 3-Butylhexahydro-1(3*H*) isobenzofuranone | 196.29 | $C_{12}H_{20}O_2$ | Leaves and stalks | [65] |
| **27** | (3*S*,3*aS*,7*aR*) 7,7*a*-Didehydro-3-butylhexahydro-1(3*H*) isobenzofuranone | 194.27 | $C_{12}H_{18}O_2$ | Leaves and stalks | [66] |
| **28** | (3*S*,3*aR*,7*aS*) 3'*S*-*β*-D-Glucopyranosyloxy, 7,7*a*-didehydrobutylhexahydro-1(3*H*) isobenzofuranone | 372.41 | $C_{18}H_{28}O_8$ | Leaves and stalks | [65] |
| **29** | (*Z*) 4,5,6,7-Tetrahydro-3-butylidene-1(3*H*) isobenzofuranone | 192.25 | $C_{12}H_{16}O_2$ | Leaves and stalks | [65] |
| **30** | (*E*) 3*S*,4,5,8-Tetrahydro-3-butylidene-1(3*H*) isobenzofuranone | 192.25 | $C_{12}H_{16}O_2$ | Leaves and stalks | [65] |
| **31** | Senkyunolide-J [syn.: (*E*) 3*S*,4,5,6,7,8-Hexahydro, 6*R*,7*R*-dihydroxy-3-butylidene-1(3*H*) isobenzofuranone] | 226.27 | $C_{12}H_{18}O_4$ | Leaves and stalks | [65] |
| **32** | Senkyunolide-N [syn.: (*E*) 3*S*,4,5,6,7,8-Hexahydro-6*S*,7*S*-dihydroxy-3-butylidene-1(3*H*) isobenzofuranone] | 226.27 | $C_{12}H_{18}O_4$ | Leaves and stalks | [65] |
| **33** | (*S*) 3-Butyl-1(3*H*) isobenzofuranone | 190.24 | $C_{12}H_{14}O_2$ | Leaves and stalks | [66] |
| **34** | 3*a*,4-Dihydro-3-(3-methylbutylidene)-1(3*H*) isobenzofuranone | 204.26 | $C_{13}H_{16}O_2$ | Leaves and stalks | [67] |
| **35** | 3-(3-Hydroxybutyl)-1(3*H*)-isobenzofuranone-*O*-*β*-D-glucopyranoside | 368.38 | $C_{18}H_{24}O_8$ | Leaves and stalks | [67] |
| **36** | 3-(3-Hydroxybutyl)-1(3*H*)-isobenzofuranone-*O*-[*β*-D-apiofuranosyl-(1→6)-*β*-D-glucopyranoside] | 500.49 | $C_{23}H_{32}O_{12}$ | Leaves and stalks | [67] |
| **37** | 3-(3-Methylbutylidene)-1(3*H*)-isobenzofuranone | 202.25 | $C_{13}H_{14}O_2$ | Leaves and stalks | [68] |

| No. | Name | Molecular weight | Molecular formula | Organ | Ref. |
|---|---|---|---|---|---|
| | **D) Sesquiterpenes** | | | | |
| **38** | *β*-Selinene | 204.35 | $C_{15}H_{24}$ | Seeds | [57] |
| **39** | *α*-Selinene | 204.35 | $C_{15}H_{24}$ | Seeds | [57] |
| **40** | *σ*- Selinene | 202.34 | $C_{15}H_{22}$ | Seeds | [57] |
| **41** | *γ*- Selinene | 204.35 | $C_{15}H_{24}$ | Seeds | [57] |
| **42** | (1*β*,4*β*)-4,14-Epoxy-1,11-eudesmanediol-11-*O*-*β*-D-glucopyranoside | 416.51 | $C_{21}H_{36}O_8$ | Seeds | [68] |
| **43** | (1*β*,4*α*,7*αH*)-1,4,11-Eudesmanetriol-11-*O*-*β*-D-glucopyranoside | 418.52 | $C_{21}H_{38}O_8$ | Seeds | [68] |
| **44** | (1*β*,2*α*)-4(15)-Eudesmene-1,2,11-triol-11-*O*-*β*-D-glucopyranoside | 416.51 | $C_{21}H_{36}O_8$ | Seeds | [68] |
| **45** | 1*β*-4(15)-Eudesmene-1,11,14-triol-11-*O*-*β*-D-glucopyranoside | 416.51 | $C_{21}H_{36}O_8$ | Seeds | [68] |
| | **E) Phthalides** | | | | |
| **46** | Sedanonic acid [syn.: 1-(1-Carboxycyclohex-l-en-6-yl) pentan-l-one] | 210.27 | $C_{12}H_{18}O_3$ | Leaves | [69, 70] |
| **47** | 1-(3-Carboxycyclohex-l-en-2-yl) pentan-l-ol | 198.26 | $C_{11}H_{18}O_3$ | Leaves | [69, 70] |
| **48** | Sedanonic anhydride | 192.25 | $C_{12}H_{16}O_2$ | Leaves | [69, 70] |
| **49** | Sedanolic acid [syn.: l-(3-Carboxycyclohex-2'"n-4-yl) pentan-l-ol] | 198.26 | $C_{11}H_{18}O_3$ | Leaves | [69, 70] |
| **50** | Sedanolide [syn.: (3-Butyl-5,6,7,7a-tetrahydrophthalide] | 194.27 | $C_{12}H_{18}O_2$ | Leaves | [69, 70] |
| **51** | 3-Isobutylidene-3a,4,5,6-tetrahydrophthalide | 192.25 | $C_{12}H_{16}O_2$ | Leaves | [69, 70] |
| | **F) Miscellaneous** | | | | |
| **52** | 2-Deoxybrassinolide | 464.70 | $C_{28}H_{48}O_5$ | Seeds | [71] |
| **53** | Anthriscinol methyl ether | 222.24 | $C_{12}H_{14}O_4$ | Seeds | [61] |
| **54** | Limonene | 136.23 | $C_{10}H_{16}$ | Leaves | [62] |
| **55** | *p*-Coumaric acid | 164.16 | $C_9H_8O_3$ | Leaves | [72] |
| **56** | Caffeic acid | 180.16 | $C_9H_8O_4$ | Leaves | [72] |
| **57** | Ferulic acid | 194.18 | $C_{10}H_{10}O_4$ | Leaves | [72] |
| **58** | Chlorogenic acid | 354.31 | $C_{16}H_{18}O_9$ | Leaves | [59] |
| **59** | Junipediol A 8-*O*-*β*-D-glucoside [syn: 2-(3,4 Dihydroxyphenyl)-3'-methyl ether-1,3-propanediol 1-*O*-*β*-D-glucopyranoside] | 360.36 | $C_{16}H_{24}O_9$ | Seeds | [73] |
| **60** | Junipediol A-4-*O*-*β*-D-glucopyranoside [syn: 2-(3,4-Dihydroxyphenyl)-3'-methyl ether-1,3-propanediol-4'-*O*-*β*-D-glucopyranoside] | 360.36 | $C_{16}H_{24}O_9$ | Seeds | [68] |
| **61** | Falcarindiol [syn: (3*R*,8*S*,9*Z*)-4,6-Diyne-3,8-diol-1,9-heptadecadiene] | 260.40 | $C_{17}H_{24}O_2$ | Roots | [74] |
| **62** | (3*R*,8*S*,9*Z*)-4,6-Diyne-3,8-diol-8-methyl ether-1,9 heptadecadiene | 274.40 | $C_{18}H_{26}O_2$ | Roots | [74] |
| **63** | 3-Methyl ether-4,5-methylenedioxy benzoic acid | 196.16 | $C_9H_8O_5$ | Seeds | [75] |
| **64** | (*R*)3-Methyl-5-propyl-2-cyclohexen-1-one | 152.23 | $C_{10}H_{16}O$ | Leaves and stalks | [76] |



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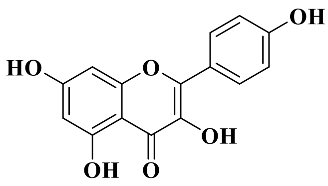

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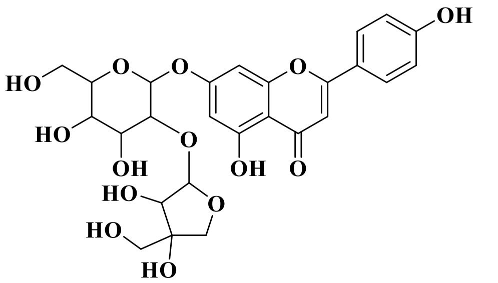

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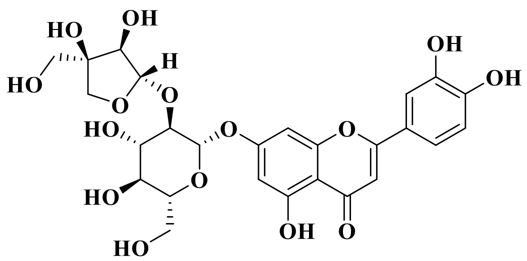

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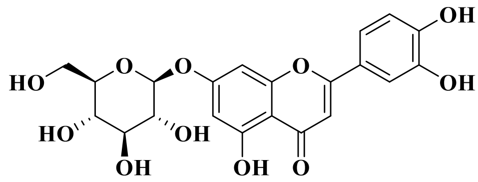

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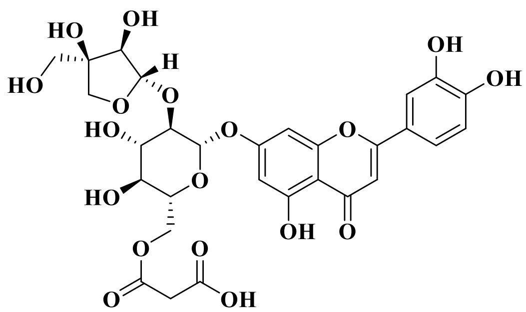

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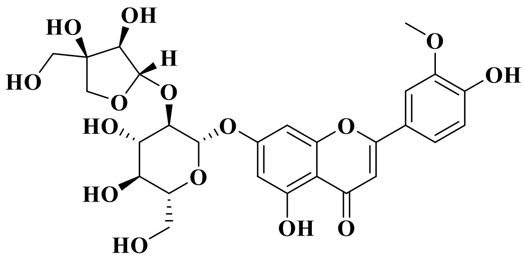

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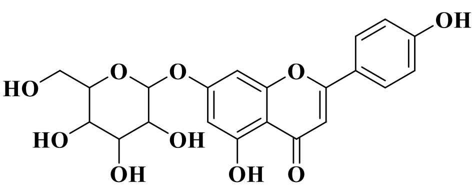

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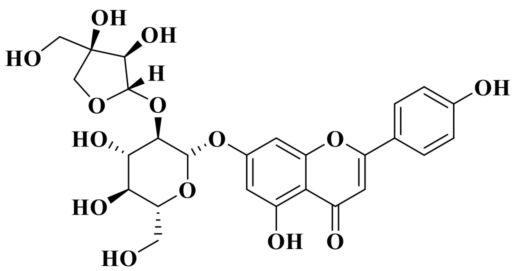

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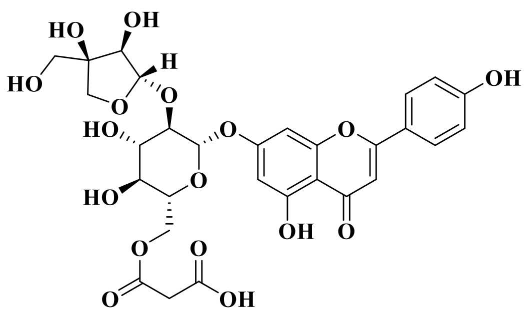

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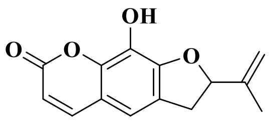
**Figure 2:** Chemical structures of the previously isolated compounds from *A.* graveolens.



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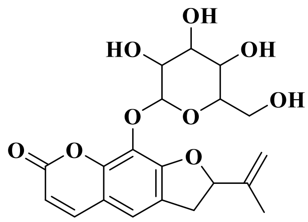

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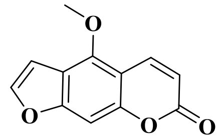

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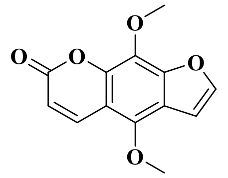

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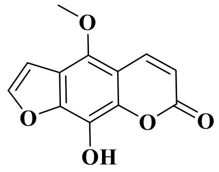

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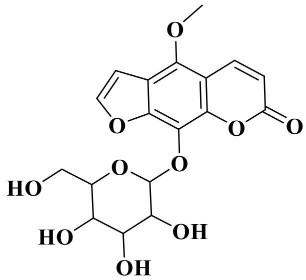

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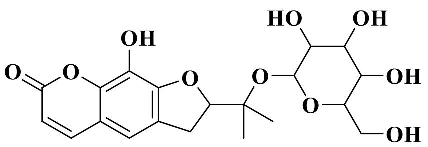

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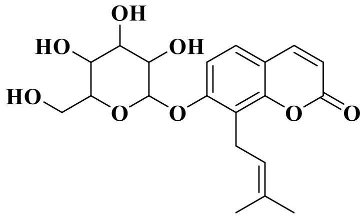

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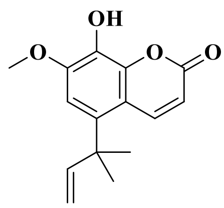

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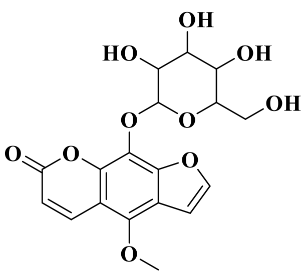

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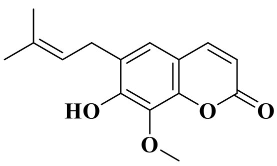

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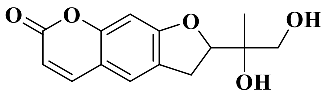

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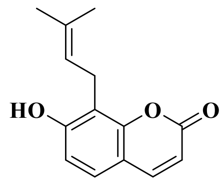

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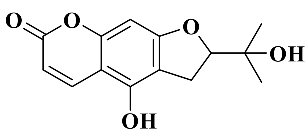

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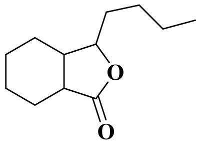

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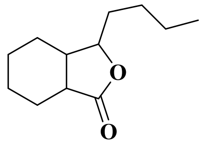

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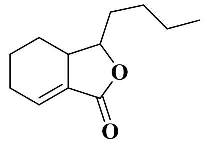

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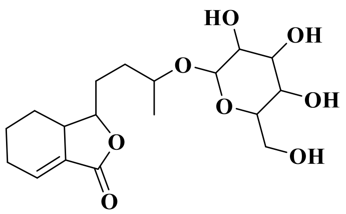

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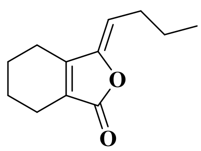

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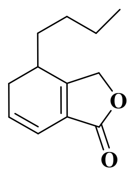

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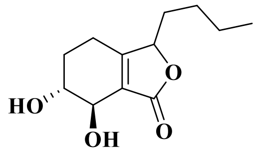

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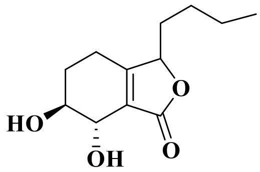
**Figure 2:** (continued).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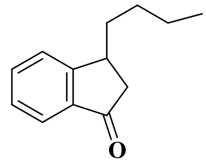
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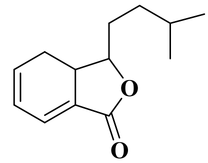
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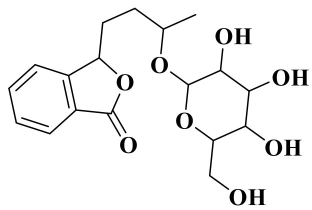
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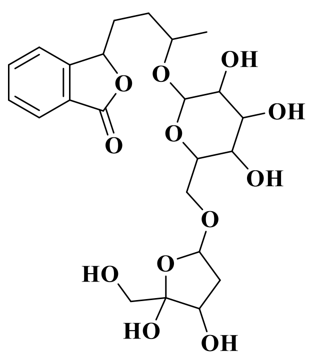
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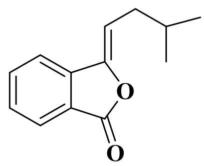
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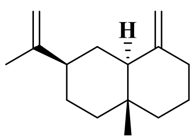
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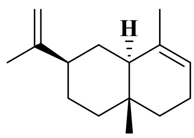
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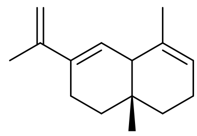
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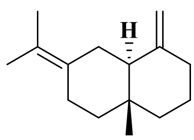
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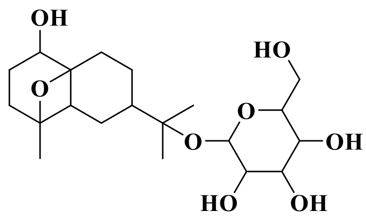
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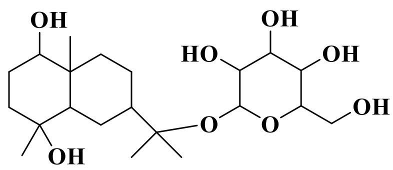
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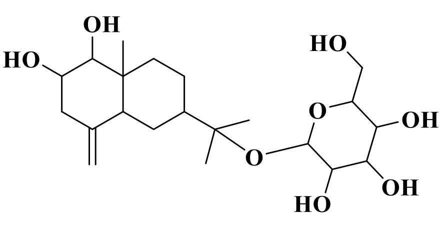
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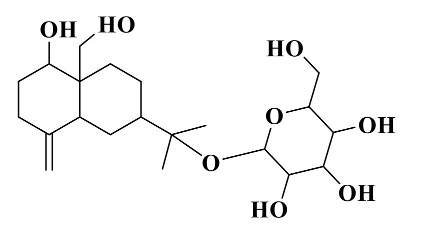
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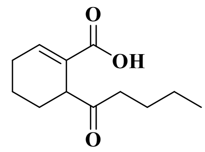
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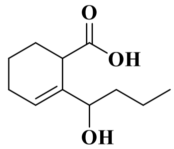
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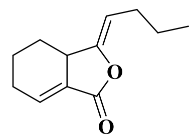
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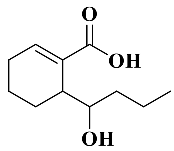
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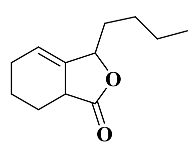
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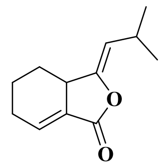
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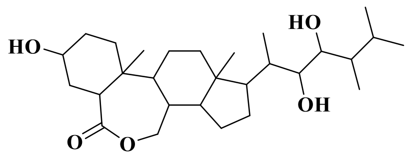
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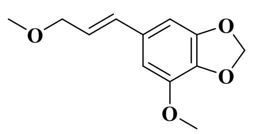
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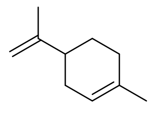
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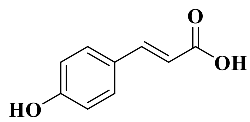
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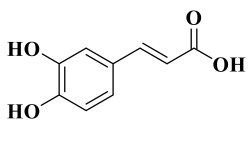
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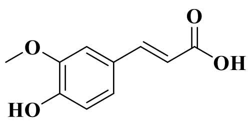
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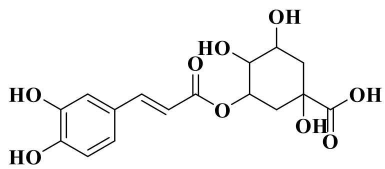
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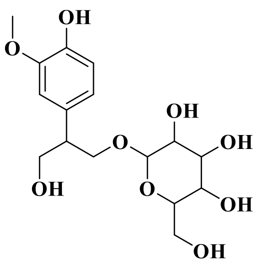
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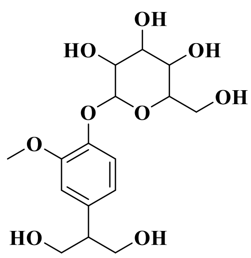
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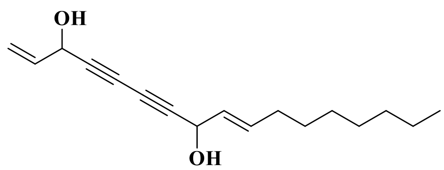
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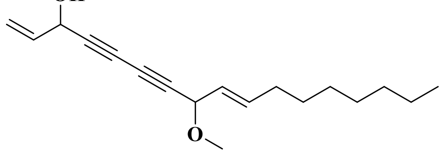
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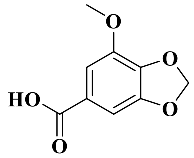
63

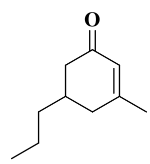
64

**Figure 2:** (continued).

Also, many biological studies have been conducted on *A. visnaga* and resulted in having antimicrobial, antidiabetic, anti-inflammatory, cytotoxic, antimutagenic, immunostimulatory, larvicidal, insecticidal, herbicidal and cardiovascular effects. Also, it causes the prevention of kidney stone formation and it has a role in the treatment of vitiligo. On the other hand, *A. graveolens* is rich in many compounds as flavonoids, coumarins, furanocoumarins, isobenzofurans, sesquiterpenes, phthalides and miscellaneous. Coumarins, isobenzofurans and flavonoids are the most commonly investigated. Leaves and seeds were investigated. Therefore, other parts need further investigation. As well, the effectiveness of *A. graveolens* has been proven as anticancer, antibacterial, antiulcerogenic, hypolipidemic and antihypertensive effects.

## Conflict of interests

The authors declare that there is no conflict of interests regarding this review.

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