Egypt. J. Chem. **Vol. 66**, No. 10 pp. 203 - 245 (2023)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Genus *Hedera*: A Comprehensive Review of its Phytoconstituents, Diverse Pharmacological Activities and Medicinal Properties

Sarah Osama[a], Moshera El Sherei[b], Dalia A. Al-Mahdy[b*], Marwa M. Refaat[c], Mokhtar Bishr[d] and Osama Salama[a#]

[a]*Department of Pharmacognosy and Medicinal Plants, Faculty of Pharmaceutical Sciences and Pharmaceutical Industries, Future University in Egypt*
[b]*Department of Pharmacognosy, Faculty of Pharmacy, Cairo University, Egypt*
[c]*Department of Microbiology and Immunology, Faculty of Pharmaceutical Sciences and Pharmaceutical Industries, Future University in Egypt*
[d]*Arab Company for Pharmaceuticals and Medicinal Plants (Mepaco), Egypt*

[#] Sadly, Prof. Osama Salama passed away in January, 2021. As this work was initiated with him, the remaining authors decided to complete the research and submit this paper as a tribute to our dear professor

Abstract

Genus *Hedera* is considered an important component of European and Asian woodlands, accounting for a large proportion of the forest understory, particularly in the British Isles. *Hedera* L.; the ivy genus, Family Araliaceae, consists of approximately 15 species. Among these, most of the detailed phytochemical and pharmacological reports are available on only a few species of the genus. Despite the long traditional and commercial use of *Hedera helix* L., the most renowned species of the genus, other species in this genus have not been reviewed properly. This review comprises the phytoconstituents, pharmacological activities and therapeutic applications of the different species of genus *Hedera.* The purpose of this work is to provide a holistic updated compile of the phytoconstituents and biological diversity of all species of genus *Hedera*, not just the well-known *H. helix*, to act as a guide for future research and pharmaceutical prospects.

Keywords: *Hedera*, Phytoconstituents; Triterpene saponins;α-hederin;*in vitro* pharmacological activities *in vivo* pharmacological activities.

1. Introduction

Since ancient times, humans have relied on plants and herbal drugs to treat many diseases and ailments. People from different civilizations have utilized plants in deliberate, researched ways over time. They possessed their own Planta Medica, as did the ancient Egyptians, Greeks, Romans, Chinese, and Indians. Herbal medicine has grown at an exponential rate over the last few decades. spreading widely in both developing and developed countries for a variety of reasons including: its natural origin, fewer side effects as well as its low cost. Many metabolites are naturally produced by plants and are commonly incorporated as: agrochemicals, flavours and colours, biopesticides, food additives as well as in the pharmaceutical industry **[7]**.

Hedera L., the ivy genus, (Family Araliaceae) consists of approximately 15 species distributed throughout North Africa, Asia, Macaronesia and Europe**[2]**. Members of the genus are highly valued as ornamentals and are frequently used in landscaping and indoors. Triterpene glycosides and phenolic compounds are the main phytoconstituents reported in species of genus *Hedera*, with numerous biological activities reported for *Hedera* species including molluscicidal, antibacterial, antiviral, antioxidant, cytotoxic, antidiabetic, hepatoprotective and anti-inflammatory activities. Because of its spasmolytic and expectorant properties, *Hedera helix* L. (Ivy leaf) was traditionally used to treat upper respiratory tract infection symptoms,**[95]** with several well-established formulations of the leaf extract

*Corresponding author e-mail: dalia.almahdy@pharma.cu.edu.eg; (Dalia A. Al-Mahdy).
EJCHEM use only: Receive Date: 26 November 2022; Revise Date: 24 January 2023; Accept Date: 30 January 2023
DOI: 10.21608/EJCHEM.2023.176914.7236
©2023 National Information and Documentation Center (NIDOC)

available commercially **[171]**. Furthermore, the German Commission E, the European Scientific Cooperative on Phytotherapy (ESCOP), and the Committee on Herbal Medicinal Products (HMPC), all have issued monographs on *H. helix***[21, 40, 41]** and approved it for treatment of symptoms of chronic inflammatory bronchial conditions as well as catarrhs of the respiratory tract. Currently, as cough is one of the early most common signs of Covid-19 infections **[148]**, *Hedera helix* is highlighted and investigated to establish potential applications in Covid-19 infections, with several recent studies suggesting that levels of evidence and safety margins reported for *Hedera helix* can merit its repurposing and prospective use as an adjuvant in the management of early and mild cases of COVID-19 **[151, 166]**.

Herein, our review highlights the phytoconstituents and pharmacological actions reported on the differentspecies of genus *Hedera*, not just the infamous *H. helix* species. The purpose of this review is to lure the attention of researchers to the vast phytochemical content and medicinal potential of the genus *Hedera* and to aid in the future utilization of its various species.

2. Search Strategy

The literature was searched electronically using Pubmed, Web of Science and Google Scholar until June 2022. Search terms included the keywords "*Hedera*", "ivy", "phytochemical", "pharmacological" and "α-hederin". There were no language restrictions during our search. For this review, phytochemical as well as *in-vitro* and *in-vivo* pharmacological studies were given priority. Searched reports are herein listed in alphabetical order of *Hedera* species names followed by a chronological order for each species.

3. Taxonomy

Despite the presence of several plant species known as Ivy e.g. Poison Ivy or Boston Ivy, the name is commonly understood to refer to plants of genus *Hedera* (Family Araliaceae), particularly the English Ivy, *H. helix***[167]**. The genus comprises about 15 species, and in spite of its vast medicinal and economic importance, its taxonomy and classification lack consensus and are considered problematic, with numerous studies attempting to distinguish between different species and to evaluate their phylogenetic relationships **[2]**. In this review, all species reported are considered accepted species and are recognized in the World Checklist and Bibliography of Araliaceae, published by the Royal Botanic Gardens, Kew **[45]**.
Reported species in this review include: *Hedera canariensis*Willd., known as Canary ivy; native to the Canary Islands, *Hedera colchica* K. Koch. (Colchis ivy), mainly growing in Georgia and Turkey, *Hedera helix*, known as Common Ivy or English ivy and widely distributed throughout the world, *Hedera nepalensis* K. Koch known as Chinese or Himalayan Ivy which is distributed in China, Nepal and the Himalayas, *Hedera rhombea* Bean. (Kizuta in Japanese) known as the Japanese ivy growing in Japan, Korea and Taiwan, *Hedera scotica* A. Cheval. (Syn. *H. helix* var. hibernica, *H.helix* var. scotica) known as Scottish or Irish ivy; a species that grows in Ireland and Scotland and finally *Hedera taurica* (Hibberd) Carr. known as Crimean ivy.

4. Phytoconstituents in Genus *Hedera*

A wide range of phytoconstituents were reported in genus *Hedera*. Triterpene saponins and phenolic compounds are among the predominant reported elements, in addition to volatile oils, polyacetylenes, norsesquiterpene glycosides, sterols, and fatty acids. Reviewed phytoconstituents in different *Hedera* species are herein presented classified according to their chemical nature.

4.1. Triterpenes

Triterpene glycosides are recognized as complex mixtures of compounds with similar chromatographic mobilities. A single organ of the plant (leaves, stems, roots, etc.) may sometimes contain several dozen glycosides.

Triterpene glycosides, present in almost all species of genus *Hedera*, comprises a large percentage of its chemical profile mostly belonging to the oleanane-type triterpenoid saponins with several reported dammarane triterpene saponins.

Alpha-hederin is considered one of the most commonly isolated triterpene glycosides from different *Hedera* species. It was isolated from *Hedera canariensis* Willd.,*H. caucasigena* Pojark., *H. colchica* K. Koch., *H. helix* L., *H. nepalensis* K. Koch., *H. pastuchovii* Woronow., *H. rhombea* (Miq.) Siebold ex Bean.,*H. scotica* A. Cheval., and *H. taurica* (Hibberd) Carr. **[190]**.

Structures of reported triterpene glycosides are presented in **Table 1** and illustrated in **Figs. 1-3**. Isolated compounds were identified using chemical transformations including acid or alkaline hydrolysis with identification of the decomposition products, in addition to extensive spectroscopic techniques including 1D and 2D ^{1}H and ^{13}CNMR spectroscopy, mass spectrometry (ESI-HR-MS) as well as literature data used to determine their structures and absolute configuration.

Table 1

Triterpene saponins identified in different species of Genus *Hedera*

Plant Species	Plant Part	Compound	Refs
Hedera canariensis Willd	Leaves	Oleanolic acid 3-*O*-*α*-L-arabinopyranoside **(1)**, Echinocystic acid 3-*O*-*α*-L-arabinopyranoside **(2)**, Hederagenin 3-*O*-*α*-L-arabinopyranoside **(3)**, Oleanolic acid 3-*O*-[*O*-*α*-L-rhamnopyranosyl-(1-2)-*α*-L-arabinopyranoside] (*β*-hederin) **(4)**, Echinocystic acid 3-*O*-[*O*-*α*-L-rhamnopyranosyl-(1-2)-*α*-L-arabinopyranoside] **(5)**, Hederagenin 3-*O*-[*O*-*α*-L-rhamnopyranosyl-(1-2)-*α*-L-arabinopyranoside] (*α*-hederin) **(6)**, Hederagenin 3-*O*-*α*-L-arabinopyranoside 28-*O*-[*O*-*α*-L-rhamnopyranosyl-(1-4)-*β*-gentiobioside **(7)**, Oleanolic acid 3-*O*-[*O*-*α*-L-rhamnopyranosyl-(1-2)-*α*-L-arabinopyranoside] 28-*O*-[*O*-*α*-L-rhamnopyranosyl-(1-4)-*β*-gentiobioside] **(8)**, Hederagenin 3-*O*-[*O*-*α*-L-rhamnopyranosyl-(1-2)-*α*-L-arabinopyranoside] 28-*O*-*β*-gentiobioside **(9)**, Hederagenin 3-*O*-[*O*-*α*-L-rhamnopyranosyl-(1-4)-*O*-*β*-gentiobiosyl-(1-4)-*O*-*α*-L-rhamnopyranosyl-(1-2)-*α*-L-arabinopyranoside **(10)**, Echinocystic acid 3-*O*-[*O*-*α*-L-rhamnopyranosyl-(1-2)-*α*-L-arabinopyranoside] 28-*O*-[*O*-*α*-L-rhamnopyranosyl- (1-4)-*β*-gentiobioside] **(11)**, Hederagenin 3-*O*-[*O*-*α*-L-rhamnopyranosyl-(1-2)-*α*-L-arabinopyranoside] 28-*O*-[*O*-*α*-L-rhamnopyranosyl-(1-4)- *β*-gentiobioside] **(12)**, Hederagenin 3-*O*-[*O*-*α*-L-rhamnopyranosyl- (1-2)-*α*-L-glucopyranoside] 28-*O*-[*O*-*α*-L-rhamnopyranosyl-(1-4)-*β*-gentiobioside] **(13)**	**[57]**
		Hederagenin 3-*O*-*α*-L-rhamnopyranosyl-(l-2)-*O*-*β*-D-glucopyranoside **(14)**, Caullophyogenin 3-*O*-*α*-L-rhamnopyranosyl-(1-2)-*O*-*α*-L-arabinopyranoside **(15)**, Caullophyogenin 3-*O*-*α*-L-rhamnopyranosyl-(1-2)-*O*-*α*-L-arabinopyranoside 28-*O*-*α*-L-rhamnopyranosyl-(1-4)-*O*-*β*-D-gentiobiosyl ester **(16)**,	**[66]**
		30-norhederagenin 3-*O*-*α*-L-rhamnopyranosyl-(1-2)-*O*-*α*-L-arabinopyranoside **(17)**, 30-norhederagenin 3-*O*-*α*-L-rhamnopyranosyl-(1-2)-*O*-*α*-L-arabinopyranoside 28-*O*-*α*-L-rhamnopyranosyl-(1-4)-*O*-*β*-D-gentiobiosyl ester **(18)**	**[159]**
		30-norhederagenin 3-*O*-*α*-L-arabinopyranosyl-28-*O*-*α*-L-rhamnopyranosyl-(1-4)-*O*-*β*-D-gentiobioside **(19)**, 30-norhederagenin 3-*O*-*α*-L-rhamnopyranosyl-(1-2)-*O*-*α*-L-arabinopyranosyl-28-*O*-*α*-L-rhamnopyranosyl-(1-4)-*O*-(6-*O*-acetyl-*β*-D-glucopyranosyl)- (1-6)-*O*-*β*-D-glucopyranoside **(20)**	**[193]**
		Oleanolic acid 3-*O*-(*α*-L-rhamnopyranosyl-(1-2)-*O*-*α*-L-arabinopyranoside)-28-*O*-[*α*-L-rhamnopyranosyl-(1-4)-*O*-(6-acetyl-*β*-D-glucopyranosyl)- (1-6)-*O*-*β*-D-glucopyranoside (Ciwujianoside C_4) **(21)**,	**[194]**

		Echinocystic acid 3-*O*-(*α*-L-rhamnopyranosyl-(1-2)-*O*-*α*-L-arabinopyranoside)-28-*O*-[*α*-L-rhamnopyranosyl-(1-4)-*O*-(6-acetyl-*β*-D-glucopyranosyl)-(1-6)-*O*-*β*-D-glucopyranoside **(22)**, Hederagenin 3-*O*-(*α*-L-rhamnopyranosyl-(1-2)-*O*-*α*-L-arabinopyranoside)-28-*O*-[*α*-L-rhamnopyranosyl-(1-4)-*O*-(6-acetyl-*β*-D-glucopyranosyl) -(1-6)-*O*-*β*-D-glucopyranoside **(23)**	
	Stems	Compounds **(2- 3**, **5-7**, **11**, and **12)** Echinocystic acid 3-*O*-*α*-L-arabinopyranoside 28-*O*-*α*-L-rhamnopyranosyl-(1-4)-*O*-*β*-D-glucopyranosyl-(1-6)-*O*-*β*-D-glucopyranoside **(24)**, Oleanolic acid 3-*O*-*β*-D-glucoronopyranoside **(25)**, Hederagenin 3-*O*-*β*-D-glucoronopyranoside **(26)**, Oleanolic acid 3-*O*-*β*-D-glucoronopyranoside 28-*O*-*α*-L-rhamnopyranosyl-(1-4)-*O*-*β*-D-glucopyranosyl-(1-6)-*O*-*β*-D-glucopyranoside **(27)**, Hederagenin 3-*O*-*β*-D-glucoronopyranoside 28-*O*-*α*-L-rhamnopyranosyl-(1-4)-*O*-*β*-D-glucopyranosyl-(1-6)-*O*-*β*-D-glucopyranoside (**28)**	**[192]**
	Roots	Compounds **(1-3**, **7**, **27**, and **28)** Hederagenin 3-*O*-*β*-D-glucopyranosyl-(1-2)-*O*-*α*-L-arabinopyranosyl-28-*O*-*α*-L-rhamnopyranosyl-(1-4)-*O*-*β*-D-glucopyranosyl-(1-6)-*O*-*β*-D-glucopyranoside **(29)**	**[195]**
Hederacaucasigena Pojark	Leaves	Compounds **(1- 8**, **11**, and **24)** Hederacaucaside D (kalopanax saponin B) **(12)**, Hederacaucaside B **(30)**, Oleanolic acid 3-*O*-*α*-L-arabinopyranoside 28-*O*-*α*-L-rhamnopyranosyl-(1-4)- *O*-*β*-D-glucopyranosyl-(1-6)-*O*-*β*-D-glucopyranoside **(31)**, Oleanolic 3- sulfate **(32)**, Echinocystic acid 3- sulfate **(33)**	**[30, 31, 50]**
Hederacolchica K. Koch.	Leaves	Hederacolchisides A1 **(34)**, A **(35)**, B, C, D **(12)**, E **(36)**, and F **(37)**	**[134]**
	Berries	Saponin 1 **(1)**, saponin B **(3)**, *α*-hederin **(6)**, hederasaponin D **(7)**, hederasaponin B **(8)**, hederasaponin C **(12)**, saponin I **(25)**, scheffleraside II **(27)**, colchiside A **(38)**, hederagenin 3-*O*-*β*-D-glucopyranoside **(39)**, hederagenin 3-*O*-*β*-D-glucopyranosyl-(1-2)- *β*-D-glucopyranoside **(40)**, oleanolic acid 3-*O*-*β*-D-glucopyranosyl-(1-2)-*β*-D-glucopyranoside (heteroside E2) **(41)**, staunoside A **(42)**, heteroside I **(43)**, and colchiside B **(44)**	**[131]**
	Stems	Compounds **(12**, **36**, and **37)** Arjunolic acid-3-*O*-*α*-D-arabinopyranoside-28-*O*-*α*-L-rhamnopyranosyl-(1-4)-*O*-*β*-D-glucopyranosyl-(1-6)-*O*-*β*-D-glucopyranoside **(45)**, Hederagenin- 3-*O*-*β*-D-xylopyranoside-28-*O*-*α*-L-rhamnopyranosyl-(1-4)-*O*-*β*-D-glucopyranosyl-(1-6)-*O*-*β*-D-glucopyranoside **(46)**	**[133]**
Hedera helix	Berries	Compounds (**3**, **6**, and **39 - 42)** Helixoside A **(43)**, helixoside B **(53)**	**[18, 83]**

	Leaves	Hederasaponins B **(8)**, C **(12)**, D **(7)**, E **(45)**, F **(47),** G (cauloside F) **(29)**, H **(48)**and I **(49)**	**[37, 119, 179]**
		Compounds **(1 - 9**, **11**, and **29)**	**[49]**
		Hederagenin 3-*O*-[*O*-α-L-rhamnopyranosyl-(1-4)-*O*-β-D-glucopyranosyl-(1-6)-*O*-β-D-glucopyranosyl-(1-4)-*O*-α-L-rhamnopyranosyl- (l-2)-α-L-arabinopyranoside **(50)**	**[157]**
		Compounds **(32 – 33**, and **47)** Echinocystic acid 3-sulfate 28-*O*-α-L-rhamnopyranosyl-(l-4)-*O*-β-D-glucopyranosyl-(1-6)-*O*-β-D-glucopyranosyl ester**(51)**, Helicoside L-8a (Oleanolic acid 3-sulfate -28-*O*- β-gentiobioside) **(52)**	**[54]**
		Hederagenin 3-*O*-β-glucoside **(39)**, hederagenin **(54),** oleanolic acid **(55)**, bayogenin **(56)**	**[116]**
Hedera helix ssp rhizomatifera	Leaves	Compounds **(6**, **8**, **12**,and **40 - 42)**	**[39]**
Hedera nepalensis K. Koch	Stem and Bark	HN-saponins B **(3)**, E **(6)**, M **(7)**, P **(12)**, N **(23)**, I **(25)**, K **(26)**, and D1 **(39)** HN-saponin F, hederagenin 3-*O*-α-L-arabinopyranosyl 28-*O*-β-D-glucopyranosyl ester **(57)**, HN-saponins H, hederagenin 28-*O*-α-L-rhamnopyranosyl-(1-4)-*O*-β-D-glucopyranosyl-(1-6)-*O*-β-D-glucopyranosyl ester **(58)**	**[101, 102]**
	Aerial parts	Compounds **(3)** andpulsatilla saponin **(6)** Lupeol **(59)**	**[112, 150]**
Hederapastuchowii	Leaves	Hederasaponin B **(8)**, hederasaponin C **(12)**, hederacolchiside E **(36)** and hederacolchiside F **(37)** Pastuchosides A **(60)**, B **(61)**, C **(62)**, D **(63)** and E **(64)**	**[132]**
Hederarhombea Bean.	Stems	Kizuta saponins K_3**(3)**, K_6 (α-hederin, **6**), K_{10}**(7)**, K_{12}**(12)**, and K_{11}**(23)**	**[161]**
	Stems and Barks	Compounds **(23)** Kizutasaponins K_2, K_4(3-*O*-acetyl-20(*S*)-dammar-24-ene-3β, 6α, 20, 26-tetraol 26-*O*-β-D-glucopyranoside **(65)**, K_5(3-oxo-20(*S*)-dammar-24-ene-6α, 20, 26-triol 26-*O*-β-D-glucopyranoside **(66)**, K_7(20(*S*)-dammar-24-ene-3β, 6α, 20, 26-tetraol 26-*O*-β-D-glucopyranoside **(67)**, K_{7a}(3-oxo-20(*S*)-dammar-24-ene-6α, 20, 21, 26-tetraol 26-*O*-β-D-glucopyranoside **(68)**, K_{7b}(20(*S*)-dammar-24-ene-3β, 6α, 20, 21, 26-pentaol 26-*O*-β-D-glucopyranoside **(69)**, K_{7c}(20(*S*)-dammar-24-ene-3β, 20, 26-triol 3, 26-di-*O*-β-D-glucopyranoside **(70)**, K_9(20(*S*)-dammar-24-ene-3β, 6α, 20, 26-tetraol 3, 26-di-*O*-β-D-glucopyranoside **(71)** K_{13}(20(*S*)-dammar-24-ene-3β, 6α, 20, 26-tetraol 3-*O*-β- sophoroside-26-*O*-β-D-	**[100, 103, 104]**

		glucopyranoside **(72)**, K_8 (Hederagenin 3-*O*-*α*-L-arabinopyranosyl 28-*O*-[*α*-L-rhamnopyranosyl-(1-4)-*O*-(6-acetyl-*β*-D-glucopyranosyl)-(1-6)-*O*-*β*-D-glucopyranosyl ester **(73)**	
		Rhombenone (27-demethyl nortriterpene) **(75)**	**[98, 201]**
	Leaves	Compounds (akeboside Stb **3**, eleutheoside K **4**, **6 -7**, **12**, glycoside L-E2 **17**, glycoside L-H3 **18**, **23**, **28**, **66 - 69**, **57**, **71**,and **73)** (24E)-26-[(*β*-D-glucopyranosyl) oxy]-6*α*, 20, 21-trihydroxydammar-24-en-3*β*-yl-*O*-*β*-D-glucopyranosyl- (1-2)-*β*-D glucopyranoside **(76)** 23-hydroxy-3*β*-[(*O*-α-L-rhamnopyranosyl-(1-2)-*α*-L-arabinopyranosyl) oxy]-11-oxo-olean-12-en-28-oic acid -*O*-*α*-L-rhamnopyranosyl-(1-4)-*O*-*β*-D-glucopyranosyl-(1-6)-*β*-D-glucopyranosyl ester **(77)**	**[201]**
Hederarhombea var. formosana	Stems and Barks	Compounds **(3**, **6 – 7**, **12**, **23**, **26**,**65 -71**, and **73)** 11*α*,12*α*-epoxy-3*β*,23-dihydroxyolean-28,13*β*-olide 3-*O*-*α*-L-arabinopyranoside **(74)**	**[177]**
Hederascotica A. Cheval.	Leaves	Compounds **(1-6**, **32 -33**, **47** and **51)**	**[51]**
Hedera taurica (Hibberd) Carr.	Berries	Compounds **(**Hederoside A3 **3**,tauroside D **5**, tauroside E **6**,hederoside G **7**, hederoside H_1 **12**,tauroside F_0 **32**, hederosideB, F, E_2 **39 -41**, hederoside I **43**,andhederoside H_2 **53)** Hederoside A_1 (Methyl ester of 3-*O*-*β*-D-glucopyranosyl hederagenin) **(78)**, Hederoside D_1 (Methyl ester of 3-*O*-[*O*-*β*-D-glucopyranosyl-(l-2)-*β*-D-glucopyranosyl] hederagenin) **(79)**, Hederoside A_2 (3-*O*-*β* D-glucopyranosyl oleanolic acid) **(80)**, Hederoside D_2 (3-*O*-[*O*-*β*-D-glucopyranosyl-(l-2)-*α*-L-arabinopyranosyl hederagenin] **(81)**,Hederacoside E_1 (Erythrodiol 3-*O*-[*O*-*β*-D-glucopyranosyl-(l~2)-*O*-*β*-glucopyranosyl]) **(82)**	**[55, 56, 59, 114, 115]**
	Stems	Compounds **(7 - 8, 12 - 13**,and **27 - 29)** 3-*O*-*β*-D-glucopyranosyl-28-*O*-[*α*-L-rhamnopyranosyl-(1-4)-*O*-*β*-D-glucopyranosyl-(1-6)-*O*-3-D-glucopyranosyl] hederagenin **(83)**, gentiobiosyl ester of hederagenin 3-O-*α*-L-arabinopyranoside **(84)**, Tauroside St-G_3; the *β*-gentiobiosyl ester of hederagenin 3-*O*-[*O*-*α*-L-rhamnopyranosyl-(1-2)-glucopyranoside] **(85)**, Hederagenin 3-*O*-(6'-*O*-ethyl *β*-D-glucopyranuronoside) 28-*O*-[*O*-*α*-L-rhamnopyranosyl-(1-4)-*O*-*β*-D-glucopyranosyl- (1-6)-glucopyranoside **(86)**, Oleanolic acid3-*O*-*β*-D-glucopyranonoside 28-*O*-[*O*-*α*-L-rhamnopyranosyl-(1-4)-*O*-(6-acetyl-*β*-D-glucopyranosyl-(1-6)-*O*-*β*-D-glucopyranoside] **(87)**, Hederagenin 3-*O*-*β*-D-glucopyranonoside 28-*O*-[*O*-*α*-L-rhamnopyranosyl-(1-4)-*O*-(6-acetyl-*β*-D-glucopyranosyl-(1-6)-*O*-*β*-D-glucopyranoside] **(88)**, Oleanolic acid 3-*O*-[*O*-*β*-D-galactopyranosyl-(1-2)-*β*-D-glucopyranuronoside 28-*β*-glucopyranoside] **(89)**,	**[62-65, 156]**

		Oleanolic acid 3-*O*-[3-D-glucopyranuronoside 28-*O*- β-gentiobioside **(90)**	
	Leaves	Compounds (leontoside A **3 - 4**, **6 – 9**, **11 -12**, **25 – 26**, **33**,vitalboside B **39**, **48**, **51**, andcauloside C **81)** Glycoside St-D_2 (hederagenin 3-*O*-[*O*-α-L-rhamnopyranosyl-(1-2)- β-D-glucopyranoside) **(91)** Glycoside St-F_2 (glycoside Rb-4) (oleanolic acid 3-*O*-[*O*-β-D-galactopyranosyl-(1-2)-O-β-D-glucopyranuronoside]) **(92)**	**[53, 60, 61, 113, 158]**

The results displayed in **Table 1** clearly revealed the species of Genus *Hedera* as a rich source of triterpene saponins. Triterpenes isolated from members of the genus mostly belong to the oleanane-type saponins with some reported constituents belonging to the dammarane type saponins and a single report of lupane-type from the aerial parts of *Hedera nepalensis*. Saponins were discovered in all organs of *Hedera* plants *viz.*, fruits, leaves, stems, barks, and roots. They were isolated in different forms including neutral monodesmoside glycosides, bisdesmoside glycosides, acidic glycosides with glucuronic acid or sulfate residues, or glycosides with acyl groups and rarely as aglycones. Dammarane triterpene saponins were exclusively reported in the leaves, stem and bark of *Hedera rhombea,* which might have a chemotaxonomic relevance in the distinction of this species. Glycosides of hederagenin, oleanolic acid and echinocystic acid aglycones were the predominant glycosides isolated from all studied species. On the other hand, glycosides of 30-norhederagenin were detected solely in the leaves of *Hedera canariensis* and *H. rhombea*, while caulophyllogenin glycosides were reported in *H. canariensis* only. It is noteworthy to mention that acidic glycosides with glucuronic acid residues were mainly detected in the stems of *Hedera* species including *H. canariensis*, *H. nepalensis*, *H. rhombea*, and *H. taurica*, while glycosides with sulfate residues were observed in the leaves of *H. caucasigena*, *H. helix*, *H. scotica*, and *H. taurica*. Finally acetylated triterpene derivatives were detected in leaves of *H. canriensis*, leaves and stem of *H. rhombea* ad stems of *H. taurica*. Whether these differences can be considered of chemotaxonomic importance to the genus, or due to lack of detailed investigation is yet to be studied.

4.2. Phenolic Compounds

Little knowledge is available on the phenolic constituents of the different species of genus Hedera, with only few species that were thoroughly investigated for their phenolic content. In fact, *Hedera helix* is considered the most studied species having undergone detailed investigation of its active constituents revealing the presence of numerous phenolic compounds along with few other species. The following section details the phenolic compounds that were isolated and identified in the different species of genus *Hedera* **(Table 2)**. Structures of reported phenolic constituents are illustrated in **Fig. 4**.

Table 2
Phenolic compounds identified in different species of Genus *Hedera*

Plant Species	Plant Part	Compound	Refs
Hedera colchica	Aerial Parts	Rutin, cyanidin-3-*O*-β-D-rutinoside	**[8]**
Hedera helix	Leaves	Phenolic acids: caffeic, chlorogenic, neochlorogenic, 3,5-*O*-dicaffeoyl-quinic, 3,4-*O*-dicaffeoylquinic, 4,5-*O*-dicaffeoylquinic, rosmarinic, protocatechuic, *p*-coumaric, and gallic acids Flavonoids: quercetin, kaempferol, rutin, hyperoside, isoquercitrin, astragalin, kaempferol 3-*O*-rutinoside, nicotiflorin Coumarins: scopolin	**[19, 116, 181, 202, 205]**
	Flowers, Fruits and Leaves	Phenolic acids: *p*-coumaric and ferulic acids Flavonoids: rutin, quercetin, and kaempferol quercitrin (flower extract)	**[137, 147]**

Hedera helix rhizomatifera	Leaves	Phenolic acids: syringaldehyde, quinic acid, di-caffeoyl quinic acid, gallic acid monohydrate Flavonoids: kampferol rhamnoside, isoquercitrin, and kaempferol-3-rutinoside Chalcone: phloretin	**[39]**
Hedera nepalensis	Leaves and Stem	Phenolic acids: quinic acid, neochlorogenic acid, chlorogenic acid, and cryptochlorogenic acid Flavonoids: rutin, hyperoside, 3,3′,4′,7-tetrahydroxyflavone, and luteolin	**[87, 200]**
	Aerial parts	Catechin and caffeic acid	**[90]**
Hedera rhombea	Leaves	Phenolic acids: caffeic acid, 3,5-dicaffeoyl quinic acid, 3-caffeoyl quinic acid, 3,4- and 4,5-di-*O*-caffeoyl quinic acids, methyl 3,4- and methyl 3,5-di-*O*-caffeoyl quinic acids Flavonoids: rutin and nicotiflorin	**[99, 111, 201]**
	Fruits	Phenolic acids: methyl 3-*O*-caffeoyl-5-*O*-*p*-coumaroylquinate and methyl 4-*O*-abscisylchlorogenate, aralianic acid, methyl 3, 5-di-*O*-caffeoylquinate, methyl 4,5-di-*O*-caffeoylquinate, 2-*O*-(3,4-dihydroxybenzoyl)-2,4, 6-trihydroxyphenylmethylacetate, 3-*O*-caffeoylquinic acid methyl ester, 5-*O*-caffeoylquinic acid methyl ester, 4-*O*-caffeoylquinic acid methyl ester, caffeic acid, caffeic acid methyl ester, 4-hydroxybenzoic acid, *p*-coumaric acid, 3,4-dihydroxybenzoic acid methyl ester, benzyl alcohol glucoside and 2-phenylethyl-6-D-glucopyranoside Cinnamoyl amino acid conjugates: N-[4′-hydroxy-(*E*)-cinnamoyl]-L-tryptophan, N-[3′,4′ -dihydroxy-(*E*)-cinnamoyl]-L-tryptophan (caffeoyl tryptophan), N-[4′ -hydroxy-(*E*)-cinnamoyl]-L-tryptophan methyl ester, N-[4′ -hydroxy-(*E*)- cinnamoyl]-L-tyrosine methyl ester and N-[3′,4′ -dihydroxy-(*E*)-cinnamoyl]-L-tryptophan methyl ester Flavonoid: quercetin	**[70]**

4.3. Polyacetylenes

Polyacetylenes are considered an interesting class of compounds that were reported exclusively in a few plant families including Araliaceae and Apiaceae. Their growth inhibitory activities and antifungal properties make them of interest to plant pathologists and pharmacologists. Polyacetylenes were reported only in *H. helix* and *H. rhombea* and interestingly falcarinol and didehydrofalcarinol, present in both species, were identified as the major allergens in ivy that have irritating properties and are moderate sensitizers **[72]**. Another interesting fact is the identification of polyacetylenes in *H. rhombea* mainly from the galled tissues induced by insect infections. Gall formation is known to cause changes in plant metabolism and could lead to isolation of new bioactive compounds **[199]**.

Polyacetylenes were reported from the stems, leaves and roots of *H. helix* including falcarinol, 11,12 dehydrofalcarinol, didehydrofalcarinol and falcarinone **[116, 153]**. Falcarinone, falcarinol and panaxydolwere also reported from the fruits **[24]**.

The insect galls on flower buds of *H. rhombea* were explored and five polyacetylenes were isolated. Their structures were interpreted using spectroscopic and chemical techniques as (*Z*)-8-acetoxy1,2-epoxy-3-oxoheptadeca-9-ene-4,6-diyne, (*Z*)- 8-acetoxy-3-oxoheptadeca-1,9-diene-4,6-diyne, (*Z*)-8-acetoxy-1-methoxy-3-oxoheptadeca-9-ene-4,6 - diyne, falcarindiol, and 8-acetoxyfalcarinol **[199]**. Twelve polyacetylenes were further isolated from the methanolic extracts of *H. rhombea* galls and identified as 8-acetoxyfalcarinol, falcarinol, ginsenoyne J, dehydrofalcarindiol, falcarindiol, crithmumdiol, PQ-2, panaxydol, PQ-6, dehydrofalcarindiol-8-acetate (8-acetoxydehydrofalcarinol), didehydrofalcarinol, and 11,12-dehydrofalcarinol. The structure-activity relationship of the isolated compounds was studied in relation to inhibition of mono- and dicotyledonous plant growth **[197]**.

From the flower buds of *H. rhombea* two new polyacetylenes were isolated. They were identified as (3*R*, 8*S*, *Z*)-3-hydroxyheptadeca-1,9-dien-4,6-diyn-8-yl 11-(1H-indol-3-yl) acetate and (9*Z*, 11*Z*)-heptadeca-1,9,11-triene-4,6-diyne-3,8-diol. **[198]**. The same group of researchers reported a new C_{17}-polyacetylene named hederyne A from the methanolic extract of *H. rhombea* galls, in addition to falcarindiol and dehydrofalcarinol. NMR, MS, IR, and UV spectroscopy were used to determine the structure of hederyne A and identified it as (*Z*)-heptadeca-9-en-4,6-diyne-1,3,8-triol **[196]**. Falcarindiol was also reported from the fruits of the plant **[70]**. Structures of reported polyacetylenes are illustrated in **Fig. 5**.

4.4. Volatile constituents

The volatile oil obtained by steam distillation of the stem and leaves of *H. helix* var. *hibernica* was analysed using GC/MS, and 17 compounds were identified. Germacrene D, *β*-caryophyllene,

sabinene, *β*-pinene, limonene, and *α*-pinene were present in the highest amounts ranging between 15.85-10.18% **[183]**. Germacrene B, *β*-elemene, *γ*-elemene (elixen), methylethyl ketone, methylisobutyl ketone, trans-2-hexanal, trans-2-hexanol, and furfurol were also reported in *H. helix***[116]**.

GC/MS analysis of the volatile oil extracted from *H. nepalensis* var. *sinensis* by hydro distillation identified twenty-one compounds. The main constituents present in the oil were phthalic di-isobutyl ester, caryophyllene oxide, sclareolide, spathulenol, *β*-caryophyllene and *α*-caryophyllene (Humulene) **[178]**.

While dynamic headspace-GC-MS analysis of the plantidentified thirty volatile constituents including thirteen terpene compounds accounting for 61.41%, where *α*-pinene and camphene accounted for 28.98% and 14.70% respectively **[125]**.

GC-MS analysis was also used to determine the essential oil composition of *H. pastuchovii*'s leaves, berries, and stems. The results revealed that the berry and leaf oils consisted mainly of sesquiterpene hydrocarbons, while monoterpene hydrocarbons predominated in the stem. The major components of the berries were 2,4-nonadienal, *β*-farnesene and carvone, while in the leaves; *p*-mentha-2,8-dien-1-ol, limonene, *β*-bisabolene, *α*-curcumene, *β*-farnesene, and *β*-sesquiphellandrene were the most abundant components.

Alpha-Pinene and limonene were the major identified constituents in the stem oil **[13]**. Structures of reported volatile constituents are illustrated in **Fig. 6**.

4.5. Miscellaneous Compounds

Fatty acids in *H. helix* were represented by petroselinic, oleic, *cis*-vaccenic, and palmitoleic acids. Petroselinic acid was present principally in the seeds, while *cis*-vaccenic, and palmitoleic acids accumulated in the pericarp **[116]**.

Only one report was found regarding the identification of alkaloids from Genus *Hedera*, where an Egyptian research group discovered the existence of the alkaloid emetine in four Egyptian varieties of *H.helix* including *H.helix* var. *baltica*, var. *hibernica*, var. *marginata* and var. *erecta***[7]**.

Free amino acids present in *H. helix* were separated, identified and their content estimated using TLC, HPLC and GC-MS. The results revealed the presence of glycine, valine, leucine, iso-leucine, proline, aspartic acid, phenyl alanine, and tyrosine. Proline was the most abundant amino acid present **[78]**.

Sterols in *H. helix* were represented by cholesterol, campesterol, stigmasterol, *β*-sitosterol and *α*-spinasterol **[7, 116]**, while a mixture of the *β*-D-glucopyranosides of stigmaterol and of *β*-sitosterol were isolated from the berries of *H. taurica* **[58]**.

Lutsenko *et al.* stated the presence of cyanidin 3-monoside, vitamins including E, C and pro-vitamin A, in addition to a carbohydtrate identified as hamamelitol (2-C-hydroxy-methyl-D-ribitol) in the leaves of *H. helix* **[116]**.

UPLC/Q-TOF-MS/MS analysis of the stems and leaves of *H. nepalensis* identified two nucleotides; adenosine and guanine **[200]**.

The carbohydrate composition of the water-soluble polysaccharide fraction of *H. pastuchovii* fruits were studied and two compounds were isolated and identified as raffinose and *O*-D-galactopyranosyl-(1-3)-*O*-D- galactopyranosyl- (1-3)-*O*-D-galactopyranosyl- (1-1) L-arabinopyranoside **[88]**.

Two norsesquiterpene glucosides identified as (6R,9R)-3-oxo-α-ionol-*β*-D glucopyranoside and (6R,9S)-3-oxo-α-ionol *β*-D-glucopyranoside were reported for the first time from the leaves of *H. rhombea* **[201]**.

The study of *H. rhombea* fruit led to the isolation of two new megastigmane glucosides denoted as hederhomoside A and B, and (6R, 9R)-3-oxo-α-ionol-*β*-D-glucopyranoside previously isolated from the leaves.

The study also identified two rare 1,4-dioxane neolignanes, as 7*R*,8′*R* -epoxy-8*R*,7′*S* -oxyneolignane, named hederhoman A and 7*S*,8′*S* -epoxy-8*R*,7′*R* - oxyneolignane, named hederhoman B alongside 4′ -dihydrophaseic acid **[70]**.

Structures of reported miscellaneous constituents are illustrated in **Fig. 7**.

5. Qualitative and Quantitative Analysis

Regarding methods of analyses of the chemical constituents of *Hedera* species, different separation, detection and quantification methods were developed and reported. Separation of the main constituents was usually acheived using HPLC/UHPLC, GC, and HPTLC methods. Detection methods including UV, DAD and MS were usually combined for the detection of marker compounds. In this section we report on the different analysis methods used for species of Genus *Hedera* focusing on analyses of triterpene saponins and phenolic constituents. Markers used for quality control or standardization included mainly *α*-hederin, hederacoside C, and hederasaponin B, in addition to rutin, quercetin, kaempferol and caffeoyl quinic acid derivatives. Amongst used techniques, HPLC-MS, UPLC-MS and GC-MS rank the top three methods in analyses of the compositions of species of genus *Hedera*, with GC-MS being especially used in analyses of volatile oil constituents.

EI-mass spectral analysis followed by CAD MIKE spectrometry (collision activated decomposition mass-analysed ion kinetic energy spectrometry) were used to detect and quantify α-hederin as well as hederacosides B and C in *H. helix* extracts and cosmetic formulations **[43]**

High-performance liquid chromatography coupled with diode array detector and UPLC–ESI–MS/MS were used for determination of *α*-hederin as well as hederacosides B and C saponins in *H. helix* leaves **[76, 136, 202]**. Another method using high resolution plate imaging technique (HPTLC) for quantification in six different subspecies of *H. helix* found that *H. helix* ssp. rhizomatifera had the highest content of *α*-hederinwhile *H. helix* ssp. Hibernica showed the highest content of hederacoside C **[160]**.

The quantitative measurement of flavonoids in ivy leaf extract and 13 commercial ivy leaf products was accomplished using HPLC coupled with a diode array detector and six compounds, including chlorogenic acid, rutin, nicotiflorin, hederacoside C, hederasaponin B, and α-hederin were quantified **[202]**

Quantitative investigation of polyphenolic compounds in *H. helix* flowers, fruits and leaves was achieved using HPLC/MS. Analysis of the non-hydrolysed extracts of flowers and fruits revealed the presence of five polyphenolic compounds *viz.*, p-coumaric and ferulic acids, rutin, quercetin and kaempferol, while quercitrin was found only in the flower extract. Four phenolic compounds: *p*-coumaric acid, ferulic acid, quercetin, and kaempferol were found in both extracts of the hydrolysed samples, while sinapic acid was only found in the extract from ivy fruit. Rutin, quercetin, and kaempferol were all present in the non-hydrolysed leaf extract, whereas only quercetin and kaempferol were found in the hydrolysed sample. Rutin was the most abundant compound in all the non-hydrolysed samples **[137, 147]**.

UPLC-ESI-MS/MS was also used to report several triterpene compounds including including *α*-hederin **(6)**, hederacoside B **(8)**, hederacoside C **(12)**, 3-*O*-*β*-D-glucopyranosyl-(1-2)-*β*-D-glucopyranosyl hederagenin **(40)**, 3-*O*-*β*-D-glucopyranosyl-(1-2)-*β*-D-glucopyranosyl oleanolic acid **(41)** and staunoside A **(42)** from *H. helix* ssp rhizomatifera leaves **[39]**.

The constituents of *H. nepalensis* stems and leaves were analysed and identified using UPLC/Q-TOF-MS/MS, and several triterpene glycosides were identified, includinghederasaponin I, hederagenin 3-*O*-*β*-D-ribopyranose-(1-3)-*α*-L-glucopyranoside-(1-2)-*α*-L-arabinopyranoside, staunoside A, pastuchoside C, hederacoside C, nor-arjunlic acid, (3*β*)-23,28-dihydroxy-28-oxoolean-12-en-3-yl-*β*-D-glucopyranosiduronic acid, *α*-hederin, 2*α*,3*β*,23-trihydroxy-12-ene-28-oleanolic acid, (2*β*,3*β*)-2,28-dihydroxy-28-oxoolean-12-en-3-yl-*β*-D-glucopyranosiduronic acid, oleanolic acid 3- *O* -*β*- D-galactopyranoside-(1-3)-*β*-D- glucopyranoside, oleanolic and ursolic acids **[200]**. The content of hederasaponin C and *α*-hederin in *H. nepalensis* was determined by means of HPLC-UV. Their percentage ranged from 0.40 – 4.01% and 0.21 to 0.54% based on absolute dry mass, respectively **[176]**.

Furthermore, a two-dimensional TLC method was proposed for identification and detection of different triterpene glycosides in *H. taurica* leaves and stem extracts *viz.*, mono- and bisdesmosidic, acidic, sulfated or acylated triterpenes using chosen solvent systems that differ in pH values **[52]**.

Quantitative investigation of polyphenolic compounds in *H. helix* flowers, fruits and leaves was achieved using HPLC/MS. Analysis of the non-hydrolysed extracts of flowers and fruits revealed the presence of five polyphenolic compounds *viz., p*-coumaric and ferulic acids, rutin, quercetin and kaempferol, while quercitrin was found only in the flower extract. Four phenolic compounds: *p*-coumaric acid, ferulic acid, quercetin, and kaempferol were found in both extracts of the hydrolysed samples, while sinapic acid was only found in the extract from ivy fruit. Rutin, quercetin, and kaempferol were all present in the non-hydrolysed leaf extract, whereas only quercetin and kaempferol were found in the hydrolysed sample. Rutin was the most abundant compound in all the non-hydrolysed samples **[137, 147]**.

The UPLC-ESI-MS/MS profile of *H. helix* rhizomatifera revealed the presence of several flavonoids and some phenolic acids. The compounds were tentatively identified as phloretin, syringaldehyde, quinic acid, kampferol rhamnoside, di-caffeoyl quinic acid, gallic acid monohydrate, isoquercitrin, and kaempferol-3-rutinoside **[39]**.

The quantitative measurement of flavonoids in ivy leaf extract and 13 commercial ivy leaf products was accomplished using HPLC coupled with a diode array detector and six compounds, including chlorogenic acid, rutin, nicotiflorin, hederacoside C, hederasaponin B, and *α*-hederin were quantified.**[202]**.

Chlorogenic acid and rutin were also identified in leaves and stem extract of *H. nepalensis* using analytical scale HPLC and LC-MS during investigation of antioxidant potential of the plant **[87]**. Moreover, UPLC/Q-TOF-MS/MS analysis of the stems and leaves of *H. nepalensis* identified several phenolic constituents including quinic acid, neochlorogenic acid, chlorogenic acid, cryptochlorogenic acid and the flavonoids; rutin, hyperoside, 3,3′,4′,7-tetrahydroxyflavone and luteolin **[200]**.

A study designed to find antioxidant constituents from the aerial parts of *H. nepalensis*,identified catechin and caffeic acid in the aqueous and the ethyl acetate fractions, respectively, using HPLC-DAD. The ethyl acetate fraction exhibited the highest flavonoids and phenolic content **[90]**.

6. Folk Uses

A wide array of traditional and folk uses was reported for several members of genus *Hedera*. Ivy leaf (*H. helix*) was mentioned in therapeutic books dating back to the 16th century for jaundice, lithiasis, dysentery and as an emmenagogue. The leaves and berries were recommended for chronic catarrh, bronchitis, and whooping cough. Externally, ivy was used for rheumatism and neuralgia and as an anti-parasitic for scabies and lice **[40]**. *Hedera colchica* was used to treat bronchospasms, inflammations and acts as a secretolytic **[131]**. Whereas the leaves and berries of *H. nepalensis* were reported to have stimulating, diaphoretic and cathartic effects. They were used for abscesses and ulcers treatment, and the leaf decoction was used to treat lice. As well, *H. nepalensis* was used in diabetes and against fever, pulmonary infections and rheumatism **[92]**. Finally, *H. rhombea* leaves were used to treat haemorrhage, chronic catarrh, jaundice, lithiasis, and convulsions**[107]**.

7. Pharmacological Activities

7.1. Molluscicidal Activity

The molluscicidal activity of *H. canariensis* was tested against *Biomphalaria alexandrina*. The results showed that *H. canariensis* was toxic to the snails after 24 hrs. The toxic action of these plants was stable against direct sunlight, but the activity was found to be reduced by both acidity (pH 4-6) and alkalinity (pH 8-10)**[36]**. The methanolic extract of *H. canariensis* leaves has been shown in another investigation to have molluscicidal properties, with the concentration of the plant extract increasing the mortality rate of exposed snails. This work used bioactivity-guided fractionation of the extract. The histological research demonstrated noticeable damage in the anatomy of the stomach and ovotestis of treated *Lymnaea cailliaudi* snails, demonstrating the activity. *Lymnaea cailliaudi* snails were more vulnerable to the methanolic extract than *B. Alexandrina* **[1]**.

The molluscicidal property of four triterpenoid saponins obtained from *H. helix* berries *viz.,* hederoside F, hederagenin 3-*O*-*β*-glucopyranoside, hederagenin-3-*O*-*α*-arabinopyranoside as well as hederagenin 3-*O*-*α*-L-rhamnopyranosyl-(1-2)-*α*-arabinopyranoside was reported against *Biomphalaria glabrata* snails. The results indicated that the saponins containing arabinose revealed stronger activity than the glucosides **[83]**.

The leaves and fruits of *H. helix* aqueous extracts were also tested against three species of experimental snails*; Biomphalaria pfeifferi*, *Bulinus sp.* and *Physa acuta* collected from Nigeria. Both extracts were potent and showed high mortality rates against all the tested snails **[188]**. Another experiment confirmed that both *α*-hederin and hederacoside F showed greater molluscicidal activity than hederacoside C against *Planorbis corneus*, *P. corneus* var. *rubra* and *Melanoides tuberculate*. The research also revealed that the glycosides' molluscicidal action was decreased when cholesterol was added, although high-potency complexes of *α*-hederin with glycine and L-alanine were reported. **[191]**.

7.2. Anti-parasitic activity

The antitrypanosomal activity of saponins obtained from *H. helix* was studied *in-vitro* and the results revealed that monodesmosides including *α*- and *δ*-hederin and aglycone hederagenin showed a mediocre level of antitrypanosomial activity against *Trypanosoma brucei brucei*, with *α*-hederin being the most effective (MIC=25 g/ml). In concentrations greater than 100 g/ml, bidesmosides such as hederacoside C and D showed no activity.**[175]**.

The anthelmintic effect of the aqueous and the hydro-alcoholic extracts of mature *H. helix* fruits was studied *in-vitro* as well as *in-vivo* against both the

eggs and adult nematode parasites of *Haemonchus contortus*. Compared to the aqueous extract, thehydro-alcoholic extract demonstrated superior *in-vitro* efficacy against adult parasites. In sheep that had been experimentally infected with *H. contortus*, two dosages of each extract's *in-vivo* anthelmintic activity were tested. The efficiency against the male parasites was improved by increasing the dose of the extracts **[35]**.

From the leaves of *H. helix*, saponin complex 60% (CS 60; containing 60% hederasaponin C, hederasaponin B and the phenolic compounds rutin, caffeic acid and chlorogenic acid), and purified saponin complex 90 % (CSP 90; containing 90% hederasaponside C accompanied by hederasaponoside B) as well as *α*-hederin were assessed for their *in-vitro* anthelminthic activity using the trematodes *Fasciola hepatica* (tape worms) and *Dicrocoelium* spp. Alpha-hederin destroyed both trematodes at doses of 0.005 and 0.001 mg/ml after being exposed for 24 hours. The same extracts were tested in naturally infected sheep for their influence on Dicrocoelium, and the worms were removed following three treatments, one of 500 and two of 800 mg/kg of CS 60 and CSP 90, but *α*-hederin was found to be less effective at the same concentrations **[7]**.

7.3. Anti-leishmanial Activity

Saponin fractions of *H. helix* including 60% saponin complex (CS 60) in addition to hederacoside B, C, and D, *α*, *β*, and *δ*-hederin, and the aglycone hederagenin were studied for their *in-vitro* antileishmanial activity on promastigote and amastigote forms of *Leishmania infantum* and *L. tropica.* On promastigote forms, monodesmosides were discovered to have comparable efficacy to pentamidine, the reference substance. Compared to the reference chemical (N-methylglucamine antimonate), hederagenin had a strong anti-amastigote impact, whereas bidesmosides had no effects **[119]**.

Alpha and betahederin obtained from *H.helix* along with hederacolchiside A1 isolated from *H. colchica*, were further tested for their *in-vitro* antileishmanial activity on *L. infantum*. By modifying membrane integrity and potential, the investigated saponins demonstrated strong antiproliferative effect on all phases of parasite growth, with hederacolchiside A1 appearing to be the most effective towards promastigotes and amastigotes **[32]**. The antileishmanial activity of the same saponins was assessed against *L. mexicana* in both promastigote and amastigote forms, and its relationship to their toxicity toward human monocytes was contrasted. Similar to previous results, saponins showed great antiproliferative effect against parasites at all stages of development, but they were very damaging to human cells **[144]**.

Contrary to previous reports, a study to ascertain the *in-vivo* efficiency of *H. helix* alcoholic extract on the experimental ulcer of zoonotic cutaneous leishmaniasis in Balb/c mice caused by *L. major* concluded that the extract in two concentrations (20% and 70%) did not decrease the size of the main lesion and amastigotes counts of the skin lesions were not reduced in the 70% concentration **[82]**.

7.4. Antimicrobial Activity

Using the agar dilution method, the *in-vitro* antifungal activity of several triterpenoid saponins including: hederagenin, *α*-hederin, *δ*-hederin, and hederasaponin C obtained from *H. helix* was studied. Derivatives of monodesmosidic hederagenin showed a wide range of effectiveness against tested *Candida* strains and dermatophyte species. *C. glabrata* was the strain that proved most susceptible, and *α*-hederin was the most active constituent **[44]**. Later the effect of *α*-hederin was investigated on *C. albicans* ultrastructure for a 24 h exposure time. Transmission electron microscopy observations showed that the compound caused changes in cellular contents as well as modifications in the cell envelope resulting in yeast degradation and eventually death. Plasma and biomembranes of *C. albicans* appears to be the primary target of *α*-hederin and the antifungal activity was confirmed at a minimal inhibitory concentration of 25 μg/ml **[130]**.

Different *H. helix* extracts were examined against various strains including *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Bacillus subtilis, Escherichia coli* as well as *Klebsiella pneumonia*. The most effective extracts against both bacteria were the ethyl acetate and methanol extracts **[185]**.

A haploinsufficiency screen was used to examine the anti-candidal mechanism of action of *α*-hederin. The results identified three genes with related functions that modulate *α*-hederin activity and the haploinsufficiency profile of the compound was found to be similar to that reported for the antifungal drug, caspofungin which works by inhibiting fungal cell wall synthesis **[139]**.

Disc diffusion method was also used in studying the antimicrobial effect of aqueous, 30% and 70% ethanolic extracts of *H. helix* leaves towards *S. aureus*, *S. epidermidis*, *E. coli*, *P. aeruginosa*, *Proteus vulgaris*, *and C. albicans.* The extracts showed dose-dependent antimicrobial activity towards all of the standard strains studied, with the

70% alcoholic extract showing the best activity against *P. aeruginosa*, *P. vulgaris and C. albicans* **[117]**.

The antimicrobial effect of the ethanolic extracts of *H. helix* leaves, flowers, immature fruits along with the ripe ones was investigated. Using the microdilution method, the activity was examined against six bacterial strains. While both immature fruit and flower extracts demonstrated strong antibacterial activity against *Listeria monocytogenes*, the immature fruit extract revealed a considerable antibacterial activity against *S. aureus*.**[138]**.

The leaves of *H. helix* were shown to have strong antibacterial action against 23 types of bacteria from 22 genera that fall into both the Gram-positive and -negative categories alongside *C. albicans*, with the activity primarily attributable to its high hederacoside C concentration.**[7, 25]**.

In another research, the 70% alcoholic leaves extract of *H. helix* showed potent antibacterial activity towards *S. epidermidis*, *S. aureus*, *P. vulgaris*, *Campylobacter jejuni* and *C. albicans* using agar disc diffusion method and compared to azithromycin and amphotericin **[203]**.

The antimicrobial potential of various subspecies of *H. helix* was tested against *C. albicans*, *B. subtilis*, and *P. aeruginosa* using HPTLC fingerprints, and the results were chemometrically analysed. In comparison to saponins, the phenolic metabolites of the various tested *H. helix* subspecies were strongly associated with antimicrobial activity, according to the study**[160]**.

Both the extract and fractions of *H. helix* were examined for their antibacterial and antifungal activities against several pathogens found in local hospitals using the agar well diffusion method.The chloroform and *n*-hexane fractions had the most potent antifungal activity against *Polyspondylium pallidum* with complete absence of fungal growth. For the antibacterial activity, the total methanolic extract revealed the greatest inhibitory activity, whereas the aqueous fraction showed the least antifungal and antibacterial activities **[143]**.

The flavonoid fraction of *H. helix* extract demonstrated promising antimicrobial activity against *K. pneumonia*, *Mycoplasma pneumoniae* and *Streptococcus pneumonia* with MICs equivalent to that of ciprofloxacin. The findings support the use of the standardized extract for acute lung injury **[162]**.

The flowers, fruits and leaves of *H. helix* were revealed to have antifungal activity against several plant fungal pathogens including *Aspergillus niger*, *Botrytis cinerea*, *Botrytis tulipae*, *Fusarium oxysporum* sp. tulipae, *Penicillium gladioli*, and *Sclerotinia sclerotiorum*. The agar dilution assay was used to measure the activity using fluconazole as the standard antifungal drug. The results were attributed to the plant's phenolic content**[137, 147]**.

Agar well diffusion assay was also used to screen *H. nepalensis* aerial parts extracted with methanol-water (80:20) against six bacterial strains; *S. aureus*, *Staphylococcus methacilline, P. aeruginosa*, *E. coli*, *Salmonella typhi*, and *Shigella flexenari*. The extract of *H. nepalensis* was found inactive against the tested bacterial strains **[186]**.

On the contrary, *H. nepalensis* ethyl acetate fraction showed activity towards *E. coli*, *K. pneumoniae* and *B. subtilis*thus proposing its potential efficiency in the treatment of gastroenteritis and pneumonia **[184]**.

In another study, the antibacterial and antifungal activities of *H. nepalensis* crude methanolic extract and different fractions were investigated, and results revealed that the chloroform fraction of the plant had good antibacterial activity (60%) against *S. aureus* whereas the remaining fractions along with the methanolic extract demonstrated moderate and low antibacterial activity. On the other hand, no fungal activity was detected against *A. niger*, *A. flavus*, *Penicillium notatum*, *Fusarium oxysporum*, *Trichoderma harzianum* and *Rhizopusstolonifer***[4]**.

The antifungal and antibacterial effects of different extracts of both the leaves and stems of *H. nepalensis* were tested against different microorganisms including *P. aeruginosa*, *Shigella sonnei*, *Enterococcus faecalis*, *K. pneumonia*, *E. coli*, *B. subtilis*, *Erwinia cartovara*, *Bacillus atrophaeus*, *Citrobacter freundii*, *Salmonella typhi*, *S. aureus*, *Bacillus cereus* and *Agrobacterium tumefacians* in addition to, *Alternaria alternate*, *A. flavus*, *P. notatum*, *A. niger*, *Trichoderma harzianum* and *C. albicans*. Maximum activity was achieved by the methanolic extract against *B. subtilis* and by both methanolic and ethanolic extracts against *K. pneumonia* and *E. coli***[145]**. Different extracts of both *H. helix* and *H. nepalensis* were also tested against various microorganisms including *S. epidermidis*, *S. aureusE. coli*, *Pseudomonas* sp. and *K. pneumoniae* and two pathogenic fungal strains (*Fusarium oxysporum* and *Penicillium* sp.). Methanolic extracts of the tested plants revealed activity towards all tested bacterial strains. In terms of fungal strains, the chloroform extract of *H. helix* inhibited *F. oxysporum*.(78%) **[20]**.

A study intended for examining the antibacterial effect of the ethanolic extracts from various *H. pastuchovii* parts including the leaves, berries and stems indicated that all the extracts revealed moderate to good activity towards both tested Gram-negative as well as Gram-positive bacteria with the leaf extract having the highest activity **[14]**.

The antimicrobial effects of three polyacetylenes obtained from the methanolic extract of *H. rhombea* galled tissue namely, hederyne A, falcarindiol and 11,12-dehydrofalcarinol were evaluated. Gram-positive and Gram-negative bacteria, along with three other fungal strains, were studied. Falcarindiol was found to be the most active compound, while hederyne A demonstrated growth inhibitory activity against some Gram-positive bacteria and fungi as well as selective antimicrobial activity towards *Micrococcus luteus***[196]**.

The aqueous extract *H. rhombea* leaves was evaluated for inhibition of *Candida* biofilm formation. Crystal violet assay was used to assess biofilm formation. The findings showed that the extract has a dose-dependent anti-biofilm formation action towards several *Candida* species, including *C. albicans*, *C. tropicalis*, *C. glabrata*, and *C. parapsilosis*, without really suppressing fungus development. *Hedera rhombea* extract also improved the antifungal activity of antibiotics and antifungal agents like miconazole and reduced fungal adherence to the host cell **[96]**.

Finally, triterpene saponins isolated from *H. taurica* were examined for their antibacterial and antifungal activity. Tauroside Sx1 (*α*-hederin) exhibited *in-vitro* antifungal activity against *C. albicans*, *C. krusei* and *C. tropicalis*, while saponins H_2 and I displayed no antimicrobial effect **[122]**. Furthermore, the sensitivity of 104 clinical isolates of different species of *Candida* to tauroside Sx1 was studied using the dilution method. The results revealed a pronounced fungicidal activity against 95 % of the isolates **[105]**. Moreover, the compound showed fungicidal activity against different *Candida* spp. **[206]**.

7.5. Antiviral Activity

H. helix extract and its isolated saponin, hederasaponin B, were tested for antiviral activity against Enterovirus 71 (EV71), the most common causesource of hand, foot, and mouth disease (HFMD). The study used cytopathic effect (CPE) reduction technique and a western blot assay to evaluate the activity towards EV71 subgenotypes C3 and C4a in vero cells. Hederasaponin B and the 30% ethanol extract of *H. helix* containing hederasaponin B were found to have significant antiviral activity. In addition to that, hederasaponin B was found to inhibit viral VP2 protein expression, implying that viral capsid protein synthesis was inhibited **[169]**.

Another study investigated the antiviral properties of *H. helix*against influenza A/PR/8 (PR8) virus. The antiviral activity of oseltamivir was significantly improved when co-administered orally with ivy extract. In PR8-infected mice, co-administration of the hedrasaponin F rich fraction of ivy extract reduced pulmonary inflammation compared to oseltamivir treatment alone. Tumor necrosis factor-alpha and chemokine (C-C motif) ligand 2 levels were also decreased after treatment, in addition to a reduction in the infiltration of two inflammatory cells typically observed in the bronchial alveolar of PR8-infected mice following virus infection **[81]**.

Using a combination of network analysis and phenotypic screening, a high content screening test aimed for the detection of anti-SARS-CoV-2 (Covid 19) compounds was carried out. Among the 65 compounds and extracts tested, *H. helix* leaves extract was found to selectively inhibit *in-vitro* infection of SARS-CoV-2. The extract reduced the viral load on infected Vero E6 cells without causing cytotoxicity at concentrations up to 50 µg/ml. The authors concluded that *H. helix* extract should be more investigated as a potential resource of antiviral compounds to be used as adjuvant therapy against SARS-CoV-2 and other viral infections **[151]**.

H. taurica's triterpene saponin, tauroside Sx1 (*α* -hederin), was found to improve mice immune responses to HIV surface glycoproteins and influenza virus **[206]**. The compound's cytotoxic activity was also evaluated against several lymphoblastoid cell lines and human peripheral blood monocytes. Also, its capability to affect HIV-1 replication was also studied, together with the capability to improve the survival of mice infected with influenza virus A/WSN/1/33(H1N1) as well as boosting the immune responses in mice immunized with an influenza vaccine.Tauroside Sx1 inhibited the MT-4 cell line and was non-toxic to all other cell lines tested. In Jurkat-tat cells, it had a moderate inhibitory effect on HIV p24 production. While oral intake of 200 g of the compound resulted in a 1.5-fold rise in survival of influenza virus-infected mice, it also increased the immunopotentiating ability of administered subunit influenza vaccine **[105]**.

7.6. Antioxidant Activity

Hederacolchisides-E and F from *H. colchica* and *α*-hederin, hederasaponin C from *H. helix* were tested for their antioxidant activity using various antioxidant assays including reducing power, total

antioxidant activity, 1,1-diphenyl-2-picryl-hydrazyl (DPPH) radical and superoxide anion radical scavenging, H_2O_2 scavenging, in addition to metal chelating activities. In comparison to reference antioxidants, all of the tested saponins demonstrated effective antioxidant activity. **[67]**.

From the berries of *H. colchica*, the antioxidant activity of the triterpenoid glycoside; 3-*O*-*β*-D-glucopyranosyl hederagenin was investigated using the aforementioned antioxidant tests. Results revealed that the compound possessed strong total antioxidant activity, reducing power, DPPH and superoxide anion radical scavenging, H_2O_2 scavenging, as well as metal chelating activities. Standard antioxidant compounds such as *α*-tocopherol and troloxwere used in the assay **[68, 71]**.

H. helix leaves' antioxidant activity was assessed in a study that tested the antioxidant activity of selected Serbian herbs using the DPPH scavenging method and the ferric-reducing antioxidant power (FRAP). Moderate activity was detected for the plant **[205]**.

Another study also used DPPH radical scavenging technique in testing the antioxidant potential of various concentrations of the crude methanol extract of *H. helix* aerial parts and subsequent solvent fractions. The results showed that the crude extract, chloroform, ethyl acetate and aqueous fractions all had significant scavenging effects in a concentration dependent manner, yet the hexane fraction had no effect **[142]**.

Algerian researchers investigated the antioxidant ability of methanolic extracts of *H. helix* leaves and other plants using three different techniques; *β*-carotene bleaching test, the 2,2-diphenyl-1-picryl-hydrazyl-hydrate free radical scavenging method and the FRAP assay. Ivyleaves revealed moderate to high activity in all assays **[149]**.

Hedera helix leaf, fruit, and flower extracts were studied for antioxidant-related chemical composition and reactivity, focusing on seasonal variation. The activity was estimated using the oxygen radical absorbance capacity (ORAC), trolox equivalent antioxidant capacity (TEAC), DPPH bleaching, and inhibition of induced *β*-carotene bleaching assays, as well as the inhibition of induced peroxidation of liposomes and the inhibition of haemoglobin ascorbate peroxidase activity (HAPX) assay. Along with the majority of performed tests, winter leaves were the most antioxidant, followed by summer leaves, and then flowers and fruits.**[128]**.

The antioxidant capacity of the ethanolic extracts from *H. helix* leaves, flowers, immature and ripe fruits was investigated. DPPH assay, total phenolic and flavonoid contents were evaluated. Findings indicated a positive correlation between antioxidant effects, polyphenolic and flavonoid contents.**[138]**.

The antioxidant effect of *H. nepalensis* crude extract, ethyl acetate and aqueous fractions was evaluated. The assay demonstrated dose-dependent free radical scavenging capacity along with a protective effect in free radical induced DNA damage assay, with the ethyl acetate and aqueous fractions exhibiting the highest activity**[92]**.

Another study investigating the radical scavenging activities of various fractions of *H. nepalensis* indicated concentration dependent nitric oxide free radical scavenging activity in the crude methanolic extract, *n*-hexane, and chloroform fractions, implying that the plant could be searched for free radical scavenging **[4]**.

The methanolic extract of *H. nepalensis* was further investigated utilizing the DNA protection, DPPH radical-scavenging, ABTS radical-scavenging, and the thiobarbituric acid-reactive substances (TBARS) assays. The two primary phenolic antioxidants were discovered to be chlorogenic acid and rutin**[87]**.

Different extracts of *H. nepalensis* leaves and stem were studied for their antioxidant activity using two different *in-vitro* techniques, the DPPH free radical and the hydrogen peroxide scavenging assays. The findings indicated that *H. neplalensis* extracts have excellent antioxidant activity **[146]**.

The antioxidant activity in addition to the total flavonoid and phenolic contents of the crude extract of *H. nepalensis* as well as its fractions; *n*-hexane, ethyl acetate and aqueous extracts, were investigated. According to the findings, the ethyl acetate fraction had the best overall antioxidant activity and reducing power when measured using the phosphomolybdenum method, which was followed by the aqueous fraction, *n*-hexane fraction, and crude extract**[90]**.

The ethanolic extracts of *H. pastuchovii* leaves, berries, and stems were screened for their total phenolic and flavonoid content in addition to their free radicals scavenging ability. Compared to leaf and stem extracts, the ethanolic extract of the berries with the highest concentrations of phenolic and flavonoid components had a discernible capacity to scavenge DPPH**[14]**.

7.7. Cytotoxic Activity

Hederacolchiside A1 isolated from *H. colchica* was testedfor its antiproliferative activity on six human

cancer cells lines including colon adenocarcinoma DLD-1, ovarian teratocarcinoma PA 1, lung carcinoma A 549, breast adenocarcinoma MCF7, prostatic adenocarcinoma PC 3 and malignant melanoma M4 Beu against normal human fibroblasts and compared to cisplatin. The investigations were carried out by means of measuring DNA content and cellular metabolic activity in living cells. Hederacolchiside A1 demonstrated strong cytotoxicity on all cancer cells.The antiproliferative effects on malignant melanoma M4 Beu *versus* normal cells suggested that even with the absence of specificity for cancer cells, hederacolchiside A1 has possible anti-tumor applications. Comparing the cytotoxicity of hederacolchiside A1 to that of five other saponins from *H. colchica* revealed new insights on structure-activity relationships**[17]**.
On cultured mouse B16 melanoma cells and non-cancer mouse 3T3 fibroblasts, the cytotoxic effects of α-hederin isolated from *H. helix* were evaluated. Proliferation of both cell types were inhibited by α-hederin at low concentrations after only 8 hours of treatment. The compound also caused cytoplasm vacuolization and membrane modifications, which resulted in cell death**[27]**.

Along with the saponin and non-saponin fractions, the methanolic extract of *H. helix* was investigated for its cytotoxicity using the brine shrimp assay. The methanolic extract of the leaves of *H. helix* was observed to have cytotoxic activity, while the saponin fraction was inactive. Additional investigation revealed that the phenolic compounds were the active constituents **[84]**.

The capability of α-hederin to enhance the efficiency of 5-fluorouracil (5-FU) was assessed. In human colon adenocarcinoma HT-29 cells, α-hederin and 5-FU were combined *in-vitro* using fixed concentration and combination index methods. It was observed that α-hederin boosted 5-FU cytotoxicity about 3.3-fold at sub-IC_{50} cytotoxic concentrations implying that α-hederin may improve colorectal cancer cell sensitivity to 5-FU **[22]**.

The cytotoxic activity of several compounds isolated from *H. helix* were tested on four mammalian cell strains. These compounds included hederacoside B, C and D in addition to α-, β- and δ-hederin together with aglycone hederagenin. They were examined on mouse 3T3 non-cancer fibroblasts, mouse B16 melanoma cells, human HeLa tumour cells, and Flow 2002 non-cancer human cells.α- and β-Hederin were the most potent compounds demonstrating cytotoxicity at a concentration of 10 μg/ml and higher. At concentrations up to 200 μg/ml, hederacoside C, B, D and hederagenin were inactive **[116, 140]**.

A study was conducted to determine the apoptosis inducing effect of hederagenin isolated from *H. helix* leaves in human colon cancer LoVo cells as well as its possible mechanism. Hederagenin strongly prevented the viability of LoVo cells in a concentration dependent method, according to the MTT assay. The induction of hederagenin significantly increased the apoptosis ratio, as did the induction of apoptotic nuclear changes.Hederagenin significantly increased reactive oxygen species generation in LoVo cells, reduced the expression of several apoptosis-associated proteins, including Bcl-2, procaspase-9, and procaspase-3, and increased polyADP-ribosepolymerase (PARP), while increasing the expression of some mediators including Bax, caspase-3, and caspase-9. The findings suggested that hederagenin could cause apoptosis in human colon cancer LoVo cells by disrupting the mitochondrial membrane**[15]**.

Hedera helix extracts were investigated for their anti-proliferative effect on two rat prostate cancer cell lines with markedly various metastatic potentials', Mat-LyLu cells (strongly metastatic) and AT-2 cells (weakly metastatic). The ethanolic extract of leaves inhibited cell kinetics (proliferation and mitotic activity) and motility in both cell lines. In Mat-LyLu cells, the ethanolic extract of the fruit inhibited cell migration, with no effect on proliferation, whereas in AT-2 cells, migration was unaffected but proliferation was inhibited. **[69]**.

The therapeutic potential of hederagenin extracted from ivy leaves in head and neck cancer (HNC) was inspected in cisplatin resistant HNC cells in addition to its possible molecular mechanisms of action. By promoting changes in mitochondrial membrane potential, hederagenin was found to selectively induce cell death in cisplatin-sensitive and cisplatin-resistant HNC cells. It also increased the production of reactive oxygen species and glutathione reduction in cancer cells through inhibiting the Nrf2-antioxidant response element (ARE) pathway and activating p53. Furthermore, the compound's selective inhibitory effects in cisplatin resistant HNC xenograft models were confirmed. According to the findings, hederagenin caused cell death in resistant HNC cells *via* the Nrf2-ARE antioxidant pathway**[97]**.

Three saponins from *H. helix* leaves including alphahederin, hederagenin, and hederacoside C were tested for their antiproliferative effect on normal fibroblasts cells and cervix epithelial tumor cells.

Results indicated that *α*-hederin had strong antiproliferative activity, while hederagenin had moderate activity and hederacoside C did not have antiproliferative activity across the entire range of concentrations **[174]**.

The cytotoxic effect of the leaves ethanolic extract of *H. helix* ssp. rhizomatifera against human hepatocellular carcinoma (HepG2) and human breast cancer cell lines (MCF7) was investigated.Results indicated that the plant exhibited a strong cytotoxic activity with IC_{50} values of 1.9125 and 2.0823 µg/ml respectively, in comparison to 1.549 and 1.02 µg/ml respectively for Doxorubicin **[39]**.

Another research used flash chromatography in fractionation of *H. helix* leaves' extract followed by testing on NCTC normal fibroblasts and antiproliferative activity on Hep-2 epithelial tumor cells. Findings revealed that the samples were biocompatible on NCTC cells up to 200 g/mL, and the saponin rich fractions had a strong antiproliferative effect on Hep-2 cells**[173]**,

Hederacolchiside A1 was tested *in-vitro* as well as *in-vivo* for its potential anti-breast cancer effect. The compound showed significant effects on several cell lines, most notably MCF-7 breast cells. It inhibited proliferation and induced apoptosis in MCF-7 cells through activating the mitochondrial apoptotic pathway and inactivating JAK2/STAT3. At both concentrations used, hederacolchiside A1 strongly inhibited the growth of transplanted tumours *in vivo***[23]**.

The methanolic extract of *H. nepalensis* leaves and stem were evaluated for brine shrimp cytotoxicity, antitumor potato disc, and radish seed phytotoxicity activity. The extracts presented significant activities with positive correlation between the three tested assays **[86]**. The potato disc antitumor assay was used to evaluate the antitumor activity of *H. nepalensis* extract and fractions. The aqueous and ethyl acetate fractions demonstrated well-defined tumour inhibition **[92]**. Another study used the brine shrimp lethality bioassay to test the cytotoxic effect of both crude methanolic extract of *H. nepalensis* along withother fractions. Findings revealed that the crude methanolic extract and chloroform fraction showed moderate brine shrimp lethality **[4]**.

Two major anticancer constituents from *H. nepalensis* were isolated and tested for growth inhibition activities on human non-small-cell lung cancer cell (A549). Hederagenin 3-*O*-*α*-L-arabinopyranoside and pulsatilla saponin A were found to be responsible for *H. nepalensis* anticancer activities. The compounds inhibited A549 cell growth by prompting cancer cell apoptosis in a dose-dependent method **[112]**.

In-vitro cancer chemopreventive and cytotoxic activities of *H. nepalensis* extract, fractions, and isolated lupeol were further investigated using nitrite, NFB, aromatase, and quinone reductase 1 (QR1) assays. The cytotoxic potential of the four samples was studied on three cancer cell lines, MCF7, MDAMB231, and HeLa, using the sulforhodamine B (SRB) assay, and all four tested samples inhibited the tested cell lines by more than 50%. Lupeol was found to be the most effective against the breast cancer cell lines MCF-7 and MDA-MB-231. Cancer chemopreventive assay results revealed that *n*-hexane, ethyl acetate fractions, and isolated lupeol have promising cancer chemopreventive potential**[89]**.

Rhombenone, a novel nortriterpene isolated from the leaves of *H. rhombea*, was able to inhibit farnesyl protein transferase enzyme (FPTase). This enzyme catalyzes a vital step in the Ras oncogene's activation and tumor formation. Compounds identified as FPTase inhibitors demonstrated high efficacy *in-vivo* against solid tumors in nude mice **[107]**.

The effects of the polyacetylenic compound, 3-hydroxyheptadeca-1,9-dien-4,6-diyn-8yl-11(1H-indol-3-yl) acetate isolated from *H. rhombea* on differentiation were investigated using the human promyelocytic leukaemia cell line HL-60. After 48 hours of treatment, cell viability decreased, followed by an increase. Microscopical examination showed that the compound induced HL-60 cells differentiation into granulocytes, as well as alterations in cell cycle kinetics and G1 phase arrest **[106]**. The HL-60 cell line was also used to explore the differentiation-inducing effect of indoleacetic acid falcarindiol ester isolated from *H. rhombea*. At 0.1 and 1.0 g/ml, the compound inhibited HL-60 cell growth and was cytotoxic at 10 g/ml. At 1.0 g/ml, it also stopped the cell cycle in the G0/G1 phase and induced granulocytic differentiation. The researchers concluded that the isolated falcarindiol derivative could be used as a chemotherapeutic agent in the treatment of human leukaemia**[182]**.

Moreover, the cytotoxic effect of 19 triterpene glycosides isolated from *H. rhombea* leaves was examined against HL-60 human promyelocytic leukemia cells. Kizutasaponin K_6 (*α*-hederin), eleutheoside K (*β*-hederin) and akeboside Stb (*δ*-hederin) demonstrated high potency with IC_{50} values of 7.2, 21.9, and 32.8 μM, respectively. *α*-Hederin was further tested against a panel of 39 cancer cell lines derived from different tissues of origin and the results demonstrated that renal ACHN, colon HCT-

116, and stomach St-4 cell lines were comparatively sensitive to the compound. Other tested compounds did not show cytotoxic activity at concentrations up to 50 μM **[201]**.

The cytotoxic and anti-proliferative activity of the triterpene saponin, tauroside Sx1 (α-hederin) obtained from *H. taurica* was studied on lymphoblastoid tumor cells of MT-4 line and fibroblast-like cells of the Vero line and the compound showed marked activity **[206]**.

The cytotoxicity of *H. pastuchovii* leaf extract and fractions against ovarian and lung cancer cell lines, as well as its genotoxicity on peripheral blood lymphocytes, were determined. Results showed that IC_{50} values in growth inhibition induced by the total extract on both cell lines were much greater than that of cisplatin's. The study established that the methanolic extract of *H. pastuchovii* leaves contained cytotoxic compounds against both ovarian and lung cell lines **[73]**.

7.8. Respiratory Effects

Hedera helix leaves have been traditionally used in herbal remedies to treat respiratory disorders for a very long time due to their expectorant and broncho-spasmolytic properties. It was also used to treat the symptoms of common cold with cough, as well as acute and chronic bronchialinflammations. The leaves and berries were administered orally as an expectorant for cough and bronchitis treatment**[7, 202]**. Nowadays, ivy leaves extracts enjoy great popularity as an effective non-antibiotic cough remedy. In 1988, a Commission monograph of the German regulatory authority authorised its use for its efficacy against respiratory tract catarrhs and chronic inflammatory bronchial conditions**[21]**.

Commercial formulations of ivy leaves are available worldwide with a long experience on the market and a wide range of published clinical studies and reviews that report and show the drug's efficacy in both children **[79, 204]** and adults suffering from respiratory diseases **[12, 16, 80, 108, 165]**. Numerous research reported the safety and tolerability of *Hedera* and its formulations **[26, 93, 171]** even for short term use during pregnancy **[9]**.

α-Hederin isolated from several *Hedera* species is included in a wide range of marketed pharmaceutical products for treating coughs **[190]**. Herein, we report on published *in-vitro* and *in-vivo* pharmacological studies that attempted to explain the mode of action of *Hedera* and its constituents in treating symptoms of both acute upper respiratory tract infections and bronchitis.

The effectiveness of *H. helix* in treating respiratory disorders is frequently credited to the presence of triterpenoidal saponins, particularly α-hederin, which has secretolytic and bronchospasmolytic properties. A study revealed that preincubating steadily transfected human kidney (HEK293) cells with 1 μM α-hederin for 24 h clearly inhibited the internalization of β_2-adrenergic receptor-GFP fusion proteins even after 20 mins stimulation with 1 μM terbutaline. α-Hederin also increased the β_2-adrenergic responsiveness in alveolar type II (A549) cells and human airway smooth muscle (HASM) cells by increasing β_2-adrenergic receptor (AR) binding and intracellular cAMP levels, which resulted in increased production and secretion of the surfactant in alveolar type II cells. As a result, an indirect β_2-mimetic mode of action can explain α-hederin's secretolytic and bronchospasmolytic effects. Hederacoside C and hederagenin, on the other hand, had no effect on receptor regulation or the binding behaviour of β_2-AR or the intracellular cAMP level **[164]**.

Isometric tension measurements by means of bovine tracheal smooth muscle strips revealed that α-hederin improved relaxation mediated by isoprenaline indirectly *via* possible inhibition of heterologous desensitisation caused by high concentrations of muscarinic ligands like methacholine in bovine tracheal smooth muscle strips. Hederacoside C or hederagenin pretreatment showed no effect on isoprenaline-induced relaxation **[189]**.

The result of oral administration of *H. helix* on lung histopathologic features was investigated and compared to the effects of dexamethasone on airway inflammation as well as remodeling in a murine model of chronic asthma. The study showed that *H. helix* administration decreased goblet cell numbers in addition to the thickness of basement membrane **[77]**.

The expectorant and antitussive activities of mixtures of *H. helix* and *Rhizoma copitidis* were investigated using citric acid -induced cough in guinea pig and phenol red secretion in mice trachea. The extracts increased tracheal secretion and inhibited coughing significantly. Equal concentrations of both extracts (1:1) at a dose of 200 mg/kg produced a more powerful influence on phenol red secretionand cough inhibition than either extract individually in a dose-dependent manner. The optimum mixing ratio was 3:1 of *H. helix* to *Rhizoma coptidis*, as it demonstrated the highest expectorant effect (27.48±4.45, p<0.001) **[170]**. The same ratio mixture of both extracts was tested for their inhibitory effects on allergic lung inflammation responses to Asian sand dust (ASD). Oral intake of the combined extract

mixture significantly inhibited the infiltration of eosinophils and lymphocytes into the allergic lung and suppressed the Th2 cell-associated cytokines and chemokines production in bronchoalveolar lavage fluid compared with positive control group **[109]**.

[48] studied the effect of different constituents of ivy leaves extract (EA 575) *viz.,* hederacoside B and *β*-hederin saponins, protocatechuic acid, neochlorogenic acid, chlorogenic acid, cryptochlorogenic acid, 3,4-, 3,5- and 4,5-dicaffeoylquinic acids, in addition to rutin, kaempferol-3-*O*-rutinoside on the β_2-adrenergic receptors of human airway smooth muscle (HASM) cells using internalization studies, fluorescence correlation spectroscopy measurements and cAMP assays, and only *β*-hederin prevented internalization of the β_2-AR under stimulating conditions and it could be considered to have a role in the β_2-mimetic effects of *H. helix.*

The influence of *α*-hederin on lung tissue pathology as well as the levels of the inflammatory mediators was assessed in a rat ovalbumin (OVA)-sensitized model of asthma. Pretreatment with α-hederin was found to affect IL-2 and IL-17 secretion pathways in addition reduced all pathological changes in pretreated groups compared to the OVA-sensitized group **[34]**.

[117] investigated in detail the impact of 70% ethanolic extract of *H. helix*leaves on both lungs and bronchi in an experimental bronchiolitis model prompted by Sephadex 50 intranasal administration. Their investigation showed that *H. helix* extract reduced dystrophy, corrected hemodynamic disorders, including oedema and hemorrhage, and decreased the bronchus reaction associated lymphoid tissue, which could be attributed to reducing macrophage cells' immunoreactivity. The mucolytic effect of the extract was elucidated by a rise in the bronchial secretory activity in addition to an increase in exudation along with the release of fluid and erythrocytes from the microvasculature. The extract's antibacterial and *in-vivo* anti-inflammatory activity endorsed its therapeutic effects on the bronchi and lung tissue. Consequently, the authors recommended it for the treatment of acute and chronic inflammation-associated bronchopulmonary infections.

In a guinea pig compressed air model, an ethanolic extract of *H. helix* leaves administered orally hindered the bronchoconstriction stimulated by ovalbumin inhalation (57% inhibition) and platelet activating factor (43% inhibition) in a dose dependent manner**[7]**.

The anti-inflammatory efficacy of *H. helix* and *Coptidis rhizoma* extracts' mixtures was tested on both neutrophilic and eosinophilicsevere asthma manifestations *via* the animal models of OVA-LPS induced neutrophilic asthma and *Aspergillus fumigatus* (Af)-induced eosinophilic asthma. Despite the effective dose of the combined extract being slightly altered depending on the asthma endotype, treatment with the extract mixture decreased both endotypes of steroid-resistant asthmatic manifestations such as airway hyper-responsiveness, pathologic changes, and the production of pro-inflammatory cytokines**[168]**.

7.9. Anti-inflammatory Activity

The anti-inflammatory effects of crude and purified saponin extracts of *H. colchica* in carrageenan- and cotton pellet-induced acute and chronic inflammation models in rats were investigated. Both extracts were found to have anti-inflammatory properties with the saponin purified extract being more effective in acute as well as chronic inflammation phases **[46]**. Similarly, both extracts from *H. helix* were tested for their anti-inflammatory activity in induced acute and chronic inflammation models. The crude saponin extract revealed higher potency against acute inflammation, while the saponin purified extract showed more potency against chronic inflammatory effect **[172]**.

In carrageenan-induced acute rat paw oedema, the acute anti-inflammatory ability of *α*-hederin and hederasaponin C obtained from *H. helix*, in addition to hederacolchisides E and -F from *H. colchica*, was evaluated. *α*-Hederin and hederasaponin C had no effect in the first phase of acute inflammation, whereas hederacolchisides E and -F revealed minor anti-inflammatory effects. Hederacolchiside F was extremely effective in the second phase, whereas *α*-hederin was ineffective. Hederasaponin C and -E showed moderate potency compared to indomethacin and hederacolchiside F **[47]**.

Another research investigated the influence of *H. helix* constituents on the activity of the hyaluronidase and elastase enzymes, which are significantly elevated in chronic inflammatory conditions such as venous insufficiency symptoms. Sapogenins from *Hedera* hindered hyaluronidase activity non-competitively and in a dose-dependent manner. Findings revealed that hederagenin and oleanolic acid had comparable IC_{50} values, whereas hederacoside C and *α*-hederin saponins were both very weak inhibitors**[42]**

The anti-inflammatory effect of *H. helix* leaves preparation containing 60-66% triterpene bidesmosidic saponins was examined at vascular level, through flow cytometry studies of VCAM-1

and ICAM-1 expression, determination of the pro-inflammatory cytokines IL6 and IL8 in extracellular environment and the VEGF factor. The extract inhibited the secretion of IL6 and IL8 and blocked the VEGF pro-angiogenic factor but had insignificant effect on the expression of adhesion molecules in bacterial inflammation. In terms of effect after TNF-stimulation, the extract inhibited IL6 and IL8 cytokines, ICAM and VCAM expression, and VEGF in a dose-dependent manner **[33]**.

In formalin-induced paw oedema, an ethanolic extract of *H. helix* was screened for anti-inflammatory activities, and an intraperitoneal injection of the extract revealed anti-inflammatory activity with 88.89% inhibition compared to the standard drug diclofenac, which revealed 94.44% inhibition. Furthermore, the extract's antiarthritic property was investigated, and a noticeable reduction in arthritic symptoms was observed**[141]**.

The influence of the dry extract obtained from ivy leaves EA 575® on the Lipopolysaccharide (LPS)-induced release of IL-6 from murine macrophages (J774.2) was investigated and compared to corticosterone as a positive control. *H. helix* leaves extract was found to decrease LPS-induced IL-6 release in a dose-dependent manner implying an anti-inflammatory effect of the extract in the treatment of chronic and acute inflammatory airway diseases accompanied by cough, as IL-6 plays an essential part in the inflammatory processes as well as the regulation of immune responses through the release of various cytokines**[154]**.

The effect of the topical application of 1% *H. helix* extract gel in comparison to 1% diclofenac gel on knee osteoarthritis was studied in a randomized clinical trial. The effects of the gels were evaluated used the visual analogue scale (VAS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and compared to a placebo gel. The research revealed that both 1% *H. helix* and diclofenac gels considerably decreased pain, morning stiffness, daytime stiffness, and physical function when compared to the placebo group (P0.05), with the 1% *H. helix* gel group reporting a greater decline in pain, morning stiffness, and daytime stiffness than the diclofenac gel group, but the difference was insignificant **[29]**.

Hederacoside C was tested for anti-inflammatory effects on *S. aureus*-induced mastitis *in-vivo* on mammary gland tissues and *in-vitro* on RAW 264.7 cells. Histopathological alterations and myeloperoxidase activity demonstrated that hederacoside C protected the mammary glands from *S. aureus*-induced tissue destruction and inflammatory cell infiltration. The compound significantly prevented the expression of anti-inflammatory cytokines, IL-6, IL-1, and TNF-*α*, while increasing IL-10, according to ELISA, western blot, and qRT-PCR results. All of the parameters examined confirmed that hederacoside-C improved mammary gland defensive system and reduced inflammation**[6]**.

Both the ethanolic extract and flavonoid fractions of *H. helix* were examined for their *in vitro* anti-arthritic effects and *in vivo* by adjuvant-induced arthritis (AIA). The ethanolic extract and flavonoid fraction significantly reduced paw oedema, as well as serum immunological indicators, inflammatory cytokines, degenerative enzymes, and reactive oxygen species indicators. According to the findings, extracts of *Hedera* leaves could be utilized to effectively treat rheumatoid arthritis **[163]**.

The anti-inflammatory, analgesic and anticonvulsant activities of *H. rhombea* leaf extracts and fractions were investigated. The methanol, butanol and ether fractions showed anti-inflammatory activity using the carrageenan induced paw edoema method, while the acetic acid induced writhing test revealed good analgesic activity but no anticonvulsant activity**[110]**.

7.10. Effects on the Digestive System

To determine the antispasmodic potential of *H. helix*, *in-vitro* antispasmodic activity on isolated guinea-pig ileum with acetylcholine as a spasmogen was performed. Saponins and phenolic compounds isolated from the plant showed substantial activity. Saponins were found to contribute the most to anti-spasmodic activity owing to their high concentration in the plant, followed by flavonols primarily kaempferol and quercitin and dicaffeoylquinic acids. In contrast to bidesmoside hederacoside C, isolated monodesmosidic saponin α-hederin and tested hederagenin exhibited significant antispasmodic activity. Flavonoid aglycones showed higher activity than their mono- or diglycosides, while B-ring monohydroxylated flavonols were more active than dehydroxylated ones. Regarding hydroxycinnamic acid derivatives, relatively low activities were observed for monocaffeoylquinic acids, rosmarinic acid and free phenolic acids, while higher values were observed for dicaffeoylquinic acids, especially 3,5- dicaffeoylquinic acid **[180]**.

On isolated rat stomach corpus and fundus strips, the effect of *α*-hederin, hederacoside C, and the total dry extract of *H. helix* on gut motility was assessed. *α*-Hederin significantly altered the spontaneous motoric activity of rat stomach smooth muscle, and its action

was concentration dependent. On the other hand, hederacoside C did not affect the motility of isolated stomach corpus and fundus strips at concentrations up to 100 M, whereas the total extract of *H. helix* produced a strong contraction comparable to the reaction induced by acetylcholine**[124]**. α-Hederin-induced contraction was revealed to be caused by calcium influx present in intercellular spaces or bound to the outside of the cell membrane. Calcium influx is primarily mediated by voltage-dependent calcium channels of the L-type**[123]**.

The ulcer preventive ability of the aqueous extracts of *H. helix* and *H. colchica* was explored in ethanol-induced ulcer model in rats. Results revealed that the extracts decreased the ulcer index and increased macroscopic curative ratio with *H. colchica* showing better activity **[135]**.

In 2018, Shah *et al*, studied the pharmacological base of *H. helix* leaves in diarrhoea and spasms. The aqueous methanolic extract provided up to 84% protection in a castor oil-induced diarrheal model in mice. It also demonstrated spasmolytic effects mediated by voltage dependent Ca^{2+} entry blockade in isolated rabbit jejunum preparations. Both activities were comparable to that of standard verapamil **[155]**.

7.11. Antidiabetic Activity

A study examined the antidiabetic effect of the aqueous and methanolic extracts of *H. helix* leaves. Both extracts were hypoglycemic and significantly reduced blood glucose levels in both normal and alloxan-induced diabetic rabbits. The hypoglycemic activity was related to the presence of significantly great amounts of hypoglycemic trace elements namely, chromium, manganese and zinc **[85]**.
H. helix aqueous extract was also assessed for antidiabetic and protective effects in normoglycemic, glucose-overloaded, and alloxan-induced rats. The extract produced a highly significant decrease in fasting and post-prandial blood sugar levels in both acute and chronic studies. *In-vitro* measurements of glycosylated haemoglobin (HbA1c) and α-glucosidase inhibitory activity also confirmed the anti-diabetic potential. When compared to the alloxan model, histopathological studies of vital organs showed that *H. helix* has a protective effect by maintaining normal architecture**[94]**.

A research was conducted to assess the *in-vitro* inhibitory effect of *H. nepalensis* along with its isolated compound on the dipeptidyl peptidase 4 (DPP-4), an important drug target for diabetes therapy. The crude extract of *H. nepalensis* possessed high inhibitory activity which was mostly retained when fractionated with ethyl acetate or *n*-hexane. The presence of DPP-4 inhibitor, the triterpenoid lupeol, contributed to the plant's anti-diabetic activity**[150]**.

The antidiabetic effect of ethanolic extracts of both leaves and stems of *H. nepalensis*was further investigated. Results proved that administration of *H. nepalensis* leaves extract considerably reduced the levels of blood glucose whereas the stem extract showed non-significant change in blood glucose levels **[145]**.

The effect of *H. nepalensis* crude extract and isolated lupeol on antioxidant defence system, biochemical parameters and behavioural indices of Alzheimer disease generated in diabetic rats was evaluated. The results revealed that the crude plant extract and lupeol significantly ameliorated the rise in plasma glucose level, improved the antioxidant enzymes profile (catalase, superoxide dismutase and reduced glutathione) in a time dependent manner and significantly normalized the increased liver function markers. When compared to the Alzheimer control group, HPLC quantification revealed a significant increase in neurotransmitter levels (dopamine and serotonin) in the midbrain region after treatment with the crude extract. The extract also reduced cognitive and memory impairment as measured by the Elevated Plus Maze (EPM) test and the Morris Water Maze (MWM). The study concluded that *H. nepalensis* showed antidiabetogenic and memory-enhancing properties and could be used to treat diseases such as Alzheimer's and diabetes **[74]**. The same group of researchers further explored the anti-diabetic effects of *H. nepalensis* crude extract, fractions, and lupeol in alloxan-induced diabetic rats. The results indicated that lupeol and *n*-hexane fraction significantly lowered the blood glucose level by increasing insulin levels in a time dependent manner as well as significantly increasing amylase and lipase activity in diabetic rats. The *n*-hexane fraction and lupeol restored suppressed antioxidant enzymes, liver and kidney functions to their normal levels **[75]**.

Another study investigated the *in-vivo* antidiabetic and wound healing potentials of the ethanolic extract of *H. nepalensis.* The extract's anti-diabetic properties were evaluated using an alloxan-induced diabetes model, while the wound healing potential was determined using an excision wound healing model. *In-vivo* antidiabetic study revealed that the extract significantly decreased the blood glucose levels in a dose and time-dependent manner and accelerated wound healing in diabetic rats. The study established that the multicomponent *H. nepalensis* crude extract could be used as a complementary therapy to manage hyperglycaemia and wounds in diabetic patients **[11]**.

In a recent study, the anti-diabetic effect of 32 isolated compounds from *H. rhombea* fruits was investigated by examining their ability to inhibit protein tyrosine phosphatase 1b (PTP1B) and *α*-glucosidase. The results showed that isolated falcarindiol and caffeoyltryptophan showed significant PTP1B inhibition. Both compounds together with *N*-[4′ -hydroxy-(*E*)- cinnamoyl]-L-tyrosine methyl ester, *N*-[3′,4′-dihydroxy-(*E*)-cinnamoyl]-L-tryptophan methyl ester, quercetin and 6-trihydroxyphenylmethylacetate displayed significant α-glucosidase inhibitions stronger than that of standard acarbose. The findings suggested that the isolated compounds could be beneficial in the treatment of type 2 diabetes **[70]**.

7.12. Hepatoprotective Activity

The impact of *α*-hederin from *Hedera* species on carbon tetrachloride (CCl_4) -induced hepatotoxicity in mice were investigated. Pre-treatment with *α*-hederin prior to CCl_4 administration was found to prohibit the increase in serum alanine aminotransferase, lactate dehydrogenase activity and lipid peroxidation; it also protected against CCl_4-induced depletion of hepatic glutathione levels although the hepatic glutathione level and glutathione-S transferase activities were not affected. α-Hederin markedly decreased the major isozyme involved in CCl_4 bioactivation, and expression; cytochrome P450 2E1. This led to a reduction of carbon tetrachloride biotransformation and as a result, protection against CCl_4-induced liver injury **[91]**.

In a CCl_4 induced rat model, the acute and chronic hepatoprotective effects of the aqueous extract of *H. helix* leaves were examined. When compared to the CCl_4 control group, pre-treatment with the extract significantly suppressed elevated serum biochemical indices such as alkaline phosphate (ALP), serum glutamate oxaloacetate transaminase (AST), serum glutamate pyruvate transaminase (ALT), and total bilirubin. Histopathological examination of liver tissues revealed that the extract reduced histological liver damage. The observed hepatoprotective effect suggested that ivy extract could be used as an adjuvant herbal hepatotonic**[3]**.

Using a mouse model, researchers also studied the protective effects of *H. helix* extract against acetaminophen-induced oxidative stress and hepatotoxicity. Treatment with *H. helix* extract reduced the levels of elevated ALP, ALT, AST, and malondialdehyde (MDA) in serum and restored the levels of catalase, glutathione peroxidase, and superoxide dismutase that had been reduced by acetaminophen administration to control levels **[126]**.

The ethanolic extract of *H. nepalensis* leaves was proved to considerably reduce the levels of bilirubin, globulin, A/G ratio, GCI level, creatinine, ALP, GGT, ALT, AST, AST/ALT ratio while increasing the total proteins and albumin. Meanwhile, stem extract of the plant revealed non-significant change in all tested enzymes **[145]**.

The hepatoprotective activity of extracts and isolated compounds from *H. rhombea* was tested in CCl_4 liver injured rats. The ethyl acetate and butanol fractions recovered elevated serum glutamic pyruvic transaminase (GPT), glutamic oxaloacetic transaminase (GOT) and γ-glutamyltranspeptidaseγ-glutamyltranspeptidase (γ-GTPγ-GTP) levels with the butanol fraction showing the maximum activity. Seven caffeoyl quinic acid derivatives isolated from the fractions were tested and the compounds significantly reduced serum GOT and GPT levels raised by CCl_4 treatment **[99]**.

6.13. Anti-mutagenic Activity

The mutagenic and antimutagenic activities of *α*, *β* and *δ*-hederin isolated from *H. helix* were examined using a modified liquid incubation technique of the Salmonella/microsomal assay. After screening against known promutagens such as benzo-[a]pyrene (BaP) and a mutagenic urine concentrate from a smoker (SU), the saponins were found non-toxic and non-mutagenic in a dose-response manner **[38]**.

In human lymphocytes, the effect of *α*-hederin on the direct clastogenicity of doxorubicin (Adriamycin®) was tested *in-vitro* for the induction of micronuclei. *α*-Hederin inhibited the clastogenicity of doxorubicin in all treatments and concentrations, with the outcomes also suggesting a desmutagenic effect. The compound appeared to activate metabolic enzymes that inactivated doxorubicin. Initial research revealed that the effective antimutagenic concentrations of *α*-hederin had no clastogenic or aneugenic effects in human lymphocytes as well as no cytotoxicity **[10]**.

The antimutagenic activity was further tested against doxorubicin in addition to carbendazim; an aneugenic agent. The results confirmed that *α*-hederin had an antimutagenic activity acting both as a desmutagenic and bioantimutagenic **[187]**.

7.14. Wound Healing Activity

The topical application of *H. helix* saponin complex containing hederacosides C, B, and *α*-hederin was found to be effective in the treatment of cellulitis, a type of liposclerosis**[118]**.

To provide evidence for the claim that triterpene saponins are effective for the treatment and prevention of venous insufficiency, a study was designed to assess the inhibitory effects of *H. helix* saponins on the activity of elastase and

hyaluronidase. The findings showed that sapogenins only were able to non-competitively inhibit hyaluronidase activity in a dose-dependent manner, while both hederacoside C and *α*-hederin were very weak inhibitors. Oleanolic acid and hederagenin, as well showed remarkable inhibition of elastase. These results provide a molecular basis for the efficacy of saponins in treatment of venous disorders by promoting the recovery of the integrity of the extracellular matrix and endothelial walls, resulting in an increase of the vascular tone, sealing effect on the pores of the luminal face of endothelium and an improvement in nutrient exchange between the microcirculatory system and the amorphous substance**[42]**.

The effect of an alcoholic extract of *H. helix* leaves on dermal collagen bundles in the wound healing process was investigated using histomorphometric and histopathological techniques. Both the 10% and 20% *H. helix* creams significantly improved collagen bundle thickness resulting in more organized collagen bundles. This could be credited to the presence of antioxidant saponins in the plant and other phytoconstituents that may act during the proliferative phase of the wound healing process **[129]**.

The wound healing properties of *H. helix* ethanolic extract of the leaves was evaluated based on the observed changes in epithelial tissue, wound healing period and histological studies on skin wounds in rats. The results displayed the absence of oedema at day 14 post lesion with reduction in vascular congestion in both tested concentrations of *H. helix* extracts, 30 and 50 mg/ml. A decrease in inflammatory cells was observed alongside an increase in fibroblasts, indicating that the lesions are becoming more chronic. Within a week of the lesion, the number of mast cells increased significantly, indicating that the extracts accelerated the healing process**[28]**.

7.15. Miscellaneous Activity

In an acetic acid-induced writhing test, the methanolic extract and subfractions of the aerial parts of *H. helix* demonstrated significant antinociceptive activity. The aqueous fraction elicited the highest effect, followed by the chloroform and ethyl acetate fractions and finally the crude methanol extract, whereas the hexane fraction had no significant effect when compared to the standard drug, diclofenac **[142]**.

The antithrombin activity of the methylene chloride and methanolic extracts of *H. helix* was tested among other plants using a chromogenic bioassay. The methylene chloride extract showed 80% activity, which could be credited to the presence of diverse classes of compounds **[120]**. Later, the composition of the methylene chloride fraction was investigated to detect the compounds responsible for the activity and 14 compounds were isolated using bioassay guided fractionation. The compounds were tested for their antithrombin activity and *β*-amyrin, stigmasterol and hexadecanoic acid showed the highest activity **[121]**.

H. helix leaves was investigated for theirantihypertensive effect *in-vivo* on normotensive and high salt-induced hypertensive Sprague-Dawley rats followed by *in-vitro* vasodilatory studies on isolated rat and rabbit aortic tissues. The crude alcoholic extract decreased blood pressure in high salt-induced hypertensive rats more than in normotensive rats. In hypertensive rats, the investigated subfractions *viz*., *n*-hexane, chloroform, ethyl acetate, and aqueous fractions were all more effective, with aqueous being the most effective and *n*-hexane the least. *In-vitro* vasodilatory studies on isolated rat and rabbit aortic tissues revealed that the crude extract and the aqueous fraction induced an endothelium-dependent effect in rat aortic rings precontracted with phenylephrine, whereas the extract and fractions produced a partial endothelium-independent effect in rat aortic rings from hypertensive rats that was unaffected by pre-treatment with L-NAME, showing endothelium dysfunction in the hypertensive rats. The extract and fractions also prevented pre-contractions brought by high K^+ levels and phenylephrine in rabbit aorta, and they altered Ca^{++} concentration-response curves. According to the findings, *H. helix* extract and fractions exhibited antihypertensive properties because of their vasodilatory effects, which are mediated *via* nitric oxide and Ca^{++} antagonistic effects **[152]**.

In a mouse model, the protective effect of *H. helix* leaf extract on paracetamol-induced oxidative stress and renal toxicity was studied. In comparison to the control group, ivy leaf extract treatment lead to a significant reduction in serum creatinine, uric acid, and serum blood urea nitrogen concentrations. The extract also reduced the histological changes caused by paracetamol, suggesting that it could be used to inhibit renal damage caused by paracetamol**[127]**.

Different reproductive parameters were used to assess the anti-androgenic and anti-spermatogenic effects of the methanolic extract of *H. nepalensis* leaves on adult male rats. *In-vitro* and *in-vivo* studies revealed a significant increase in oxidative stress with decreased antioxidant activity at the highest dose regimens. Improved ROS production and lipid peroxidation cause DNA damage in rat sperm. *In-vivo* measurements of sperm parameters revealed significantly decreased levels of sperm viability,

motility, and daily sperm production (DSP) in treated animals, while histopathological analysis revealed decreased epithelial height and a wider lumen with fewer spermatozoa in high-dose-treated groups (150 mg/kg). Testosterone concentrations decreased significantly in all extract-treated groups, whereas plasma LH and FSH levels decreased only in high-dose-treated groups. The methanolic extract of *H. nepalensis* leaves may impair male fertility by causing hormonal imbalance and oxidative stress, which may result in histological changes, sperm DNA damage, and finally spermatogenic arrest **[5]**.

8. Conclusion

The genus *Hedera* comprises 15 species, however, till this day, there are no published comprehensive review articles comprising the traditional uses, phytochemistry, and pharmacological activities of different species of the genus. The current review on phytoconstituents, *in-vitro* as well as *in-vivo* pharmacological activities and therapeutic importance of different species of genus *Hedera* revealed a wide range of bioactive chemical constituents including triterpene glycosides which are present in almost all species of genus *Hedera*. And although other constituents may have shown various significant bioactivities, the triterpenes are the major active principles in all members of this genus and could be used as chemotaxonomic markers for the genus.

To date, 92 triterpene compounds and their derivatives **(1-92)** were reported from various species of genus *Hedera* with *α*- hederin being the most isolated triterpene from almost all species, followed by phenolic compounds, polyacetylenes and volatile oils. The highest number of different classes of triterpenes were isolated from the leaves followed by berries and stems and finally the roots. Detailed investigations on triterpenes profile of some *Hedera* species is required to determine its full phytochemical profile and to determine its potential utilization in the future. These poorly investigated species include: *Hedera caucasigena* Pojark, the roots of *H. colchica* where it is considered the only un-investigated part of the plant with no reported phytochemical constituents and *Hedera pastuchowii* where despitethe low number of trials, the findings revealed interesting results.

More studies on the phenolic composition of various species of genus *Hedera* are required to fully understand the chemical profile of the genus. Rutin in addition to quinic and caffeic acids were the main phenolic compounds found in *H. helix, H. colchica*, *H. rhombea* whereas other *Hedera* species were not investigated for their phenolic content. Polyacetylenes were only studied in *H. helix* and *H. rhombea* which is considered missing work for future perspective for researchers as polyacetylenes are considered important bioactive components with various biological activities including antitumor, immunomodulatory, neuroprotective, hypoglycemic, antiviral, antibacterial, antifungal, hepatoprotective as well as renoprotective activities.

Finally, it is evident that phytocompounds isolated from the *Hedera* genus exhibited a myriad of medicinal activities, however some species were investigated more than others, despite having similar chemical profiles. This merits further systematic investigations of the chemical constituents of members of *Hedera* genus to obtain novel bioactive molecules with new pharmacological applications. It is also essential to investigate and explore other untouched species of the genus for the future discovery and development of new drugs that can be incorporated in the pharmaceutical industry.

9. Conflicts of Interests

The authors have no relevant financial or non-financial interests to disclose.

10. Funding

No funding was received to assist with this manuscript preparation

11. References

[1] Abdel Rahman, E.H. and S.E. Hassan, Molluscicidal saponins from leaves of *Hedera canariensis*. Journal of the Egyptian Society of Parasitology, 2008. 38(1): p. 293-304.

[2] Ackerfield, J. and J. Wen, A morphometric analysis of Hedera L.(the ivy genus, Araliaceae) and its taxonomic implications. Adansonia, 2002. 24(2): p. 197-212.

[3] Adil, A., S.S. Khan, S. Naeem, R. Ikram, and N. Jaffer, Evaluation of acute and chronic hepatoprotective activity of *Hedera helix* L. Aqueous leaf extract on carbon tetrachloride-induced hepatotoxicity in rat model. Pak. J. Phytopathol, 2017. 34: p. 1-15.

[4] Ahmad, B., N. Munir, S. Bashir, S. Azam, I. Khan, and M. Ayub, Biological screening of *Hedera nepalensis*. J. Med. Plant Res, 2012. 6(39): p. 5250-5257. DOI: https://doi.org/10.5897/JMPR12.244.

[5] Ain, Q.U., M. David, M.U. Ijaz, and S. Jahan, Assessment of antiandrogenic and antispermatogenic activity of *Hedera nepalensis* in adult male rats. Andrologia,

2022. 54(3): p. e14353. DOI: https://doi.org/10.1111/and.14353.

[6] Akhtar, M., A. Shaukat, A. Zahoor, Y. Chen, Y. Wang, M. Yang, T. Umar, M. Guo, and G. Deng, Hederacoside-C inhibition of *Staphylococcus aureus*-induced mastitis via TLR2 & TLR4 and their downstream signaling NF-κB and MAPKs pathways *in vivo* and *in vitro*. Inflammation, 2020. 43(2): p. 579-594. DOI: https://doi.org/10.1007/s10753-019-01139-2.

[7] Al-Snafi, A.E., Pharmacological and therapeutic activities of *Hedera helix*. A review J. Pharm. Pharmacol, 2018. 8(5): p. 41-53.

[8] Alaniya, M.D., N.S. Kavtaradze, and A.V. Skhirtladze, Anthocyan glycoside from *Hedera colchica*. Chem. Nat. Compd, 2008. 44(5): p. 673-674. DOI: https://doi.org/10.1007/s10753-019-01139-2.

[9] Alkattan, A., R. Alameer, E. Alsalameen, M. Almaary, M. Alkhairat, A. Alkhalifah, F. Alghanim, and N. Radwan, Safety of English ivy (*Hedera helix*) leaf extract during pregnancy: retrospective cohort study. DARU, 2021. 29(2): p. 493-499. DOI: https://doi.org/10.1007/s40199-021-00415-7.

[10] Amara-Mokrane, Y.A., M. Lehucher-Michel, G. Balansard, G. Duménil, and A. Botta, Protective effects of *α*-hederin, chlorophyllin and ascorbic acid towards the induction of micronuclei by doxorubicin in cultured human lymphocytes. Mutagenesis, 1996. 11(2): p. 161-167. DOI: https://doi.org/10.1093/mutage/11.2.161.

[11] Asif, M., M. Zafar, M. Saleem, M. Saadullah, S.H. Khalid, M.S.S. Khan, Z. Iqbal, I.U. Khan, L. Hussain, and H.S. Yaseen, Evaluation of antidiabetic and wound healing properties of ethanol extract of *Hedera nepalensis* in alloxan-induced diabetic rats. S. Afr. J. Bot, 2022. 146: p. 118-126. DOI: https://doi.org/10.1016/j.sajb.2021.10.007.

[12] Baharara, H., A.T. Moghadam, A. Sahebkar, S.A. Emami, T. Tayebi, and A.H. Mohammadpour, The Effects of Ivy (*Hedera helix*) on Respiratory Problems and Cough in Humans: A Review. Natural Products and Human Diseases, 2021: p. 361-376. DOI: https://doi.org/10.1007/978-3-030-73234-9_23.

[13] Baharfar, R., R. Azimi, Z. Rahmani, and A. Naqinezhad, Chemical Composition of the Essential Oils from Leaves, Berries, and Stems of Hedera pastuchovii. Chemistry of Natural Compounds, 2017. 53(1): p. 162-164.

[14] Baharfar, R., Z. Rahmani, M. Mohseni, and R. Azimi, Evaluation of the antioxidant and antibacterial properties of ethanol extracts from berries, leaves and stems of *Hedera pastuchovii* Woron. ex Grossh. Nat. Prod. Res, 2015. 29(22): p. 2145-2148. DOI: https://doi.org/10.1080/14786419.2014.994211.

[15] Bao-Xin-Zi, L., Z. Jin-Yong, L. Yu, Z. Xi, W. Jian, G. Jun-Fei, Y. Jia-Rui, Z. Bing-Jie, F. Liang, and J. Xiao-Bin, Hederagenin from the leaves of ivy (*Hedera helix* L.) induces apoptosis in human LoVo colon cells through the mitochondrial pathway. BMC Cmplementary and Alternative Medicine, 2014. 14(1): p. 1-10. DOI: https://doi.org/10.1186/1472-6882-14-412.

[16] Barnes, L.A.J., M. Leach, D. Anheyer, D. Brown, J. Carè, R. Lauche, D.N. Medina, T.A. Pinder, A. Bugarcic, and A. Steel, The effects of *Hedera helix* on viral respiratory infections in humans: A rapid review. Adv Integr Med, 2020. 7(4): p. 222-226. DOI: https://doi.org/10.1016/j.aimed.2020.07.012.

[17] Barthomeuf, C., E. Debiton, V. Mshvildadze, E. Kemertelidze, and G. Balansard, *In vitro* activity of hederacolchisid A1 compared with other saponins from *Hedera colchica* against proliferation of human carcinoma and melanoma cells. Planta Med, 2002. 68(08): p. 672-675. DOI: https://doi.org/10.1055/s-2002-33807.

[18] Bedir, E., H. Kirmizipekmez, O. Sticher, and I. Caliş, Triterpene saponins from the fruits of *Hedera helix*. Phytochemistry, 2000. 53(8): p. 905-9. DOI: https://doi.org/10.1016/s0031-9422(99)00503-8.

[19] Bezruk, I., V. Georgiyants, and L. Ivanauskas, Comparison of components profile in herbal raw material, extract and pharmaceuticals of *Hedera helix*. ScienceRise: Pharmaceutical Science, 2020. 4(26): p. 36-39. DOI: https://doi.org/10.15587/2519-4852.2020.210768.

[20] Bibi, Y., J. Naeem, K. Zahara, M. Arshad, and A. Qayyum, *In Vitro* Antimicrobial Assessment of Selected Plant Extracts from Pakistan. Iran J Sci Technol Trans A Sci, 2018. 42(1): p. 267-272. DOI: https://doi.org/10.1007/s40995-018-0498-8.

[21] Blumenthal, M., W.R. Busse, A. Goldberg, J. Gruenwald, T. Hall, C.W. Riggins, and R.S. Rister, The complete german commission E monographs. Therapeutic guide to herbal medicines. American Botanical Council. Integr, 1998. DOI: https://doi.org/10.7326/0003-4819-130-5-199903020-00024.

[22] Bun, S., R. Elias, B. Baghdikian, J. Ciccolini, E. Ollivier, and G. Balansard, *α*-hederin potentiates 5-FU antitumor activity in human colon adenocarcinoma cells. Phytother Res, 2008. 22(10): p. 1299-1302. DOI: https://doi.org/10.1002/ptr.2483.

[23] Chen, A., S. Zhang, D. Zhang, X. Hu, N. Xu, J. Li, Q. Zhang, J. Lu, and X. Wu, Anti-Proliferative and Pro-Apoptotic Activities of Hederacolchiside A1 On MCF-7 Cells Via ROS Regulation and JAK2/STAT3 Inactivation. Research Square, 2021: p. 1-17. DOI: https://doi.org/10.21203/rs.3.rs-408362/v1.

[24] Christensen, L.P., J. Lam, and T. Thomasen, Polyacetylenes from the fruits of *Hedera helix*. Phytochemistry, 1991. 30(12): p. 4151-4152. DOI: https://doi.org/10.1016/0031-9422(91)83484-3.

[25] Cioaca, C., C. Margineanu, and V. Cucu, The saponins of *Hedera helix* with antibacterial activity. Die Pharmazie, 1978. 33(9): p. 609-610.

[26] Costa, A.R., Â. Jesus, A. Cardoso, A. Meireles, A. Colaço, and A. Cruz, Efficacy and safety of dry extract *Hedera helix* in the treatment of productive cough. BMC Health Services Research, 2016. 16: p. 120-120. DOI: http://dx.doi.org/10.1186/s12913-016-1423-5.

[27] Danloy, S., J. Quetin-Leclercq, P. Coucke, M. De Pauw-Gillet, R. Elias, G. Balansard, L. Angenot, and R. Bassleer, Effects of *α*-hederin, a saponin extracted from *Hedera helix*, on cells cultured *in vitro*. Planta Med, 1994. 60(01): p. 45-49. DOI: https://doi.org/10.1055/s-2006-959406.

[28] De Moraes Palma, F.A., A.R. Da Mata, I. De Almeida Rocha, L. Martim, D.B. Repeke, S.E. Esposito, L.F. Pereira, and C.E.P. Repeke, Study of wound healing in rat skin treated with extract of *Hedera helix* L. Braz. J. Dev., 2021. 7(12): p. 115126-115139. DOI: https://doi.org/10.34117/bjdv7n12-330.

[29] Dehghan, M., M. Saffari, M. Rafieian-kopaei, A. Ahmadi, and Z. Lorigooini, Comparison of the effect of topical *Hedera helix* L. extract gel to diclofenac gel in the treatment of knee osteoarthritis. J Herb Med, 2020. 22: p. 100350. DOI: https://doi.org/10.1016/j.hermed.2020.100350.

[30] Dekanosidze, G.E., T.T. Gorovits, T.A. Pkheidze, and É.P. Kemertelidze, Kalopanax saponin B from *Hedera caucasigena*. Chem. Nat. Compd, 1970. 6(4): p. 511-511.

[31] Dekanosidze, G.E., T.A. Pkheidze, and É.P. Kemertelidze, Triterpene glycosides of *Hedera caucasigena*. Chem. Nat. Compd, 1970. 6(3): p. 383-383. DOI: https://doi.org/10.1007/BF00567340.

[32] Delmas, F., C. Di Giorgio, R. Elias, M. Gasquet, N. Azas, V. Mshvildadze, G. Dekanosidze, E. Kemertelidze, and P. Timon-David, Antileishmanial activity of three saponins isolated from ivy, *α*-hederin, *β*-hederin and hederacolchiside A1, as compared to their action on mammalian cells cultured *in vitro*. Planta Med, 2000. 66(04): p. 343-347. DOI: https://doi.org/10.1055/s-2000-8541.

[33] Dumitriu, B., L. Olariu, R. Nita, L. Zglimbea, and N. Rosoiu, Vascular anti-inflammatory effects of natural compounds from *Aesculus hippocastanum* and *Hedera helix*. Rom Biotech Lett, 2013. 18(1): p. 7963-7974.

[34] Ebrahimi, H., M. Fallahi, A.M. Khamaneh, M.A. Ebrahimi Saadatlou, S. Saadat, and R. Keyhanmanesh, Effect of *α*-Hederin on IL-2 and IL-17 mRNA and miRNA-133a Levels in lungs of ovalbumin-sensitized male rats. Drug Dev. Res, 2016. 77(2): p. 87-93. DOI: https://doi.org/10.1002/ddr.21292.

[35] Eguale, T., G. Tilahun, A. Debella, A. Feleke, and E. Makonnen, Haemonchus contortus: *in vitro* and *in vivo* anthelmintic activity of aqueous and hydro-alcoholic extracts of *Hedera helix*. Exp. Parasitol, 2007. 116(4): p. 340-345. DOI: https://doi.org/10.1016/j.exppara.2007.01.019.

[36] El-Emam, M.A., S.M. El-Amin, and W.S. Ahmed, Molluscicidal properties of the plants *Cestrum parqui* (Fam. *Solanaceae*) and *Hedera canariensis* (Fam. *Araliaceae*). Egypt J Bilharz, 1990. 12(1-2): p. 185-195.

[37] Elias, R., A.M.D. Lanza, E. Vidal-Ollivier, G. Balansard, R. Faure, and A. Babadjamian, Triterpenoid Saponins from the Leaves of *Hedera helix*. J. Nat. Prod, 1991. 54(1): p. 98-103. DOI: https://doi.org/10.1021/np50073a006.

[38] Elias, R., M.D. Meo, E. Vidal-Ollivier, M. Laget, G. Balansard, and G. Dumenil, Antimutagenic activity of some saponins isolated from *Calendula officinalis* L., *C. arvensis* L. and *Hedera helix* L. Mutagenesis, 1990. 5(4): p. 327-332. DOI: https://doi.org/10.1093/mutage/5.4.327.

[39] Elsohafy, S., S. Shams, S. Sallam, and R.A. Nassra, Phytochemical investigation and cytotoxic activity of *Hedera helix* ssp rhizomatifera leaves. Records of

Pharmaceutical and Biomedical Sciences, 2020. 4(2): p. 68-77. DOI: https://dx.doi.org/10.21608/rpbs.2020.32829.1069.

[40] EMA/HMPC. *Assessment Report on Hedera helix L., Folium.* 2017 [cited 2022 June]; Available from: https://www.ema.europa.eu/en/documents/herbal-report/final-assessment-report-hedera-helix-l-folium-revision-2_en.pdf.

[41] ESCOP, *ESCOP Monographs: The Scientific Foundation for Herbal Medicinal Products*. 2nd edition ed. 2003: European Scientific Cooperative on Phytotherapy, Exeter (UK): ESCOP, Stuttgart: Georg Thieme Verlag, New York: Thieme New York.

[42] Facino, R.M., M. Carini, R. Stefani, G. Aldini, and L. Saibene, Anti-elastase and anti-hyaluronidase activities of saponins and sapogenins from *Hedera helix*, *Aesculus hippocastanum*, and *Ruscus aculeatus*: factors contributing to their efficacy in the treatment of venous insufficiency. Archiv der Pharmazie, 1995. 328(10): p. 720-724. DOI: https://doi.org/10.1002/ardp.19953281006.

[43] Facino, R.M., M. Carini, P. Traldi, B. Pelli, B. Gioia, and E. Arlandini, Confirmative assay and quantitative determination of *Hedera Helix* L. saponins (*α*-hederin, hederacosides B and C) in raw plant extracts and in cosmetic formulations by EI and CAD MIKE spectrometry. Biomed. environ. mass spectrom, 1987. 14(4): p. 187-194. DOI: https://doi.org/10.1002/bms.1200140409.

[44] Favel, A., M.D. Steinmetz, P. Regli, E. Vidal-Ollivier, R. Elias, and G. Balansard, *In vitro* antifungal activity of triterpenoid saponins. Planta Med, 1994. 60(01): p. 50-53. DOI: https://doi.org/10.1055/s-2006-959407.

[45] Frodin, D.G. and R. Govaerts, *World checklist and bibliography of Araliaceae*. 2003: Royal Botanic Gardens.

[46] Gepdiremen, A., V. Mshvildadze, H. Süleyman, and R. Elias, Acute and chronic antiinflammatory effects of *Hedera colchica* in rats. J. Ethnopharmacol, 2004. 94(1): p. 191-195. DOI: https://doi.org/10.1016/j.jep.2004.06.001.

[47] Gepdiremen, A., V. Mshvildadze, H. Süleyman, and R. Elias, Acute anti-inflammatory activity of four saponins isolated from ivy: alpha-hederin, hederasaponin-C, hederacolchiside-E and hederacolchiside-F in carrageenan-induced rat paw edema. Phytomedicine, 2005. 12(6-7): p. 440-444. DOI: https://doi.org/10.1016/j.phymed.2004.04.005.

[48] Greunke, C., A. Hage-Hülsmann, T. Sorkalla, N. Keksel, F. Häberlein, and H. Häberlein, A systematic study on the influence of the main ingredients of an ivy leaves dry extract on the *β*2-adrenergic responsiveness of human airway smooth muscle cells. Pulm, 2015. 31: p. 92-98. DOI: https://doi.org/10.1016/j.pupt.2014.09.002.

[49] Grishkovets, V., A. Kondratenko, N. Tolkacheva, A. Shashkov, and V.Y. Chirva, Triterpene glycosides of *Hedera helix* I. The structures of glycosides L-1, L-2a, L-2b, L-3, L-4a, L-4b, L-6a, L-6b, L-6c, L-7a, and L7-b from the leaves of common ivy. Chem. Nat. Compd, 1994. 30(6): p. 689-692. DOI: https://doi.org/10.1007/BF00630604.

[50] Grishkovets, V.I., Triterpene glycosides from *Hedera caucasignena* leaves. Chem. Nat. Compd, 1999. 35(6): p. 688-689. DOI: https://doi.org/10.1007/BF02236308.

[51] Grishkovets, V.I., Triterpene glycosides from *Hedera scotica* leaves. Chem. Nat. Compd, 1999. 35(6): p. 690-691.

[52] Grishkovets, V.I., Triterpene Glycosides Analyzed by Two-Dimensional Thin-Layer Chromatography. Chem. Nat. Compd, 2001. 37(1): p. 57-60. DOI: https://doi.org/10.1023/A:1017654610794.

[53] Grishkovets, V.I., S.V. Godin, O.Y. Tsvetkov, A.S. Shashkov, and V.Y. Chirva, Triterpene glycosides of *Hedera taurica* XVI. Structures of glycosides St-A, St-B1, St-B2, St-C, St-D1, St-D2, St-E, St-F1, and St-F2 from the stems of Crimean ivy. Chem. Nat. Compd, 1997. 33(3): p. 316-319. DOI: https://doi.org/10.1007/BF02234884.

[54] Grishkovets, V.I., A.E. Kondratenko, A.S. Shashkov, and V.Y. Chirva, Triterpene glycosides of *Hedera helix* III. Structure of the triterpene sulfates and their glycosides. Chem. Nat. Compd, 1999. 35(1): p. 70-72.

[55] Grishkovets, V.I., A.A. Loloiko, A.S. Shashkov, and V.Y. Chirva, Triterpene glycosides of *Hedera taurica* VI. Structures of hederosides G, H1, H2, and I from the berries of Crimean ivy. Chem. Nat. Compd, 1990. 26(6): p. 663-666. DOI: https://doi.org/10.1007/BF00630077.

[56] Grishkovets, V.I., A.A. Loloiko, A.S. Shashkov, and V.Y. Chirva, Triterpene glycosides of *Hedera taurica.* V. Structure of hederosides C and E1 from Crimean ivy berries. Chem. Nat. Compd, 1990. 26(2): p. 186-189. DOI: https://doi.org/10.1007/BF00607540.

[57] Grishkovets, V.I., D.Y. Sidorov, L.A. Yakovishin, N.N. Arnautov, A.S. Shashkov, and V.Y. Chirva, Triterpene glycosides of

Hedera canariensis. I. Structures of glycosides LA, LB1, LB2, LC, LD, LE1, LG1, LG2, LG3, LG4, LH1, LH2, And LI1 from the leaves of *Hedera canariensis*. Chem. Nat. Compd, 1996. 32(3): p. 360-365. DOI: https://doi.org/10.1007/BF01372340.

[58] Grishkovets, V.I., N.V. Tolkacheva, A.S. Shashkov, and V.Y. Chirva, Triterpene glycosides of *Hedera taurica* VII. Structures of taurosides A and D from the leaves of Crimean ivy. Chem. Nat. Compd, 1991. 27(5): p. 603-606. DOI: https://doi.org/10.1007/BF00630363.

[59] Grishkovets, V.I., N.V. Tolkacheva, A.S. Shashkov, and V.Y. Chirva, Triterpene glycosies of *Hedera taurica* VIII. Taurosides F1, F2, and F3 and a triterpenoid sulfate. Chem. Nat. Compd, 1991. 27(6): p. 760-761. DOI: https://doi.org/10.1007/BF00629952.

[60] Grishkovets, V.I., N.V. Tolkacheva, A.S. Shashkov, and V.Y. Chirva, Triterpene glycosides of *Hedera taurica*. Chem. Nat. Compd, 1992. 28(5): p. 455-460. DOI: https://doi.org/10.1007/BF00630649.

[61] Grishkovets, V.I., N.V. Tolkacheva, A.S. Shashkov, and V.Y. Chirva, Triterpene glycosides of *Hedera taurica* X. Structures of compounds F 4, I, and J from the leaves of Crimean ivy. Chem. Nat. Compd, 1992. 28(6): p. 593-596. DOI: https://doi.org/10.1007/BF00630436.

[62] Grishkovets, V.I., O. Tsvetkov, A.S. Shashkov, and V.Y. Chirva, Triterpene glycosides from *Hedera taurica*. XIII. Structure of taurosides St-I1 and St-I2 from Crimean ivy stems. Bioorganicheskaia khimiia, 1995. 21(6): p. 468-473.

[63] Grishkovets, V.I., O.Y. Tsvetkov, S.V. Godin, A.S. Shashkov, and V.Y. Chirva, Triterpene glycosides of *Hedera taurica* XV. Structures of glycosides St-I3, St-I4a, St-I4b, and St-I5 from the stems of Crimean ivy. Chem. Nat. Compd, 1997. 33(3): p. 310-315. DOI: https://doi.org/10.1007/BF02234883.

[64] Grishkovets, V.I., O.Y. Tsvetkov, A.S. Shashkov, and V.Y. Chirva, Triterpene glycosides of *Hedera taurica* XIV. Structures of glycosides St-G0–2, St-J, and St-K from the stems of Crimean ivy. Chem. Nat. Compd, 1997. 33(3): p. 305-309. DOI: https://doi.org/10.1007/BF02234882.

[65] Grishkovets, V.I., O.Y. Tsvetkov, A.S. Shashkov, N.V. Tolkacheva, and V.Y. Chirva, Triterpene glycosides of *Hedera taurica* II. Structures of taurosides St-G0–1, St-G2, and St-G3 from the stems of Crimean ivy. Chem. Nat. Compd, 1994. 30(6): p. 772-773. DOI: https://doi.org/10.1007/BF00630624.

[66] Grishkovets, V.I., L.A. Yakovishin, I.N. Shchipanova, A.S. Shashkov, and V.Y. Chirva, Triterpene glycosides of *Hedera canariensis* III. Determination of the structures of glycosides LF1, LF2, and LI2 from the leaves of Algerian ivy. Chem. Nat. Compd, 1998. 34(6): p. 694-698.

[67] Gülçin, İ., V. Mshvildadze, A. Gepdiremen, and R. Elias, Antioxidant Activity of Saponins Isolated from Ivy: *α*-Hederin, Hederasaponin-C, Hederacolchiside-E and Hederacolchiside-F. Planta Med, 2004. 70(06): p. 561-563. DOI: https://doi.org/10.1055/s-2004-827158.

[68] Gülçin, İ., V. Mshvildadze, A. Gepdiremen, and R. Elias, The Antioxidant Activity of a triterpenoid glycoside isolated from the berries of *Hedera colchica*: 3-O-(*β*-d-glucopyranosyl)-hederagenin. Phytother Res, 2006. 20(2): p. 130-134. DOI: https://doi.org/10.1002/ptr.1821.

[69] Gumushan-Aktas, H. and S. Altun, Effects of *Hedera helix* L. extracts on rat prostate cancer cell proliferation and motility. Oncol, 2016. 12(4): p. 2985-2991. DOI: https://doi.org/10.3892/ol.2016.4941.

[70] Ha, M.T., T.H. Lee, C.S. Kim, R. Prajapati, J.A. Kim, J.S. Choi, and B.S. Min, PTP1B and *α*-glucosidase inhibitory activities of the chemical constituents from *Hedera rhombea* fruits: Kinetic analysis and molecular docking simulation. Phytochemistry, 2022. 197: p. 113100. DOI: https://doi.org/10.1016/j.phytochem.2022.113100.

[71] Hamed, M.M., L.A. Refahy, and A.A. Shafei, *In vitro* cytotoxic activity and antioxidant potential of different extracts from *Pittosporum eugenioides*. Egyptian Journal of Chemistry, 2022. 65(8): p. 1-3. DOI: https://dx.doi.org/10.21608/ejchem.2022.113405.5189.

[72] Hansen, L. and P.M. Boll, Polyacetylenes in *Araliaceae*: their chemistry, biosynthesis and biological significance. Phytochemistry, 1986. 25(2): p. 285-293. DOI: https://doi.org/10.1016/S0031-9422(00)85468-0.

[73] Hashim, K., *Effect of fractioned leaves extract of Hedera pastuchovii on cytotoxicity in cancer cell line (MCF-7, Hela) and genotoxicity effects on lymphocytes*. 2018.

[74] Hashmi, W., H. Ismail, F. Mehmood, and B. Mirza, Neuroprotective, antidiabetic and antioxidant effect of *Hedera nepalensis* and

lupeol against STZ+ AlCl 3 induced rats model. DARU journal of pharmaceutical sciences, 2018. 26(2): p. 179-190. DOI: https://doi.org/10.1007/s40199-018-0223-3.

[75] Hashmi, W.J., H. Ismail, L. Jafri, and B. Mirza, Ethnopharmacological activity of *Hedera nepalensis* K. Koch extracts and lupeol against alloxan-induced type I diabetes. Braz. J. Pharm. Sci, 2020. 56. DOI: https://doi.org/10.1590/s2175-97902019000318406.

[76] Havlíková, L., K. Macáková, L. Opletal, and P. Solich, Rapid determination of α-hederin and hederacoside C in extracts of Hedera helix leaves available in the Czech Republic and Poland. Natural product communications, 2015. 10(9): p. 1934578X1501000910.

[77] Hocaoglu, A.B., O. Karaman, D.O. Erge, G. Erbil, O. Yilmaz, B. Kivcak, H.A. Bagriyanik, and N. Uzuner, Effect of *Hedera helix* on lung histopathology in chronic asthma. Iranian Journal of Allergy, Asthma and Immunology, 2012: p. 316-323.

[78] Hodisan, T., M. Culea, C. Cimpoiu, and A. Cot, Separation, identification and quantitative determination of free amino acids from plant extracts. Journal of Pharmaceutical and Biomedical Analysis, 1998. 18(3): p. 319-323. DOI: https://doi.org/10.1016/S0731-7085(98)00094-6.

[79] Hofmann, D., M. Hecker, and A. Völp, Efficacy of dry extract of ivy leaves in children with bronchial asthma–a review of randomized controlled trials. Phytomedicine, 2003. 10(2-3): p. 213-220. DOI: https://doi.org/10.1078/094471103321659979.

[80] Holzinger, F. and J.F. Chenot, Systematic review of clinical trials assessing the effectiveness of ivy leaf (*Hedera helix*) for acute upper respiratory tract infections. Evidence-Based Complementary and Alternative Medicine, 2010. 2011. DOI: https://doi.org/10.1155/2011/382789.

[81] Hong, E.H., J.H. Song, A. Shim, B.R. Lee, B.E. Kwon, H.H. Song, Y.J. Kim, S.Y. Chang, H.G. Jeong, and J.G. Kim, Coadministration of *Hedera helix* L. extract enabled mice to overcome insufficient protection against influenza A/PR/8 virus infection under suboptimal treatment with oseltamivir. PloS one, 2015. 10(6): p. e0131089. DOI: https://doi.org/10.1371/journal.pone.0131089.

[82] Hooshyar, H., S. Talari, and F. Feyzi, Therapeutic effect of *Hedera helix* alcoholic extract against cutaneous leishmaniasis caused by Leishmania major in Balb/c mice. Jundishapur Journal of Microbiology, 2014. 7(4). DOI: https://doi.org/10.5812/jjm.9432.

[83] Hostettmann, K., Saponins with molluscicidal activity from *Hedera helix* L. Helvetica Chimica Acta, 1980. 63(3): p. 606-609. DOI: https://doi.org/10.1002/hlca.19800630307.

[84] Ibrar, M., I. Ilahi, and F. Hussain, The cytotoxic potential of ivy (*Hedera helix* L.) leaves. Pak. J. Bot, 2001. 33: p. 237-242.

[85] Ibrar, M., I. Ilahi, and F. Hussain, Hypoglycemic activity of *Hedera helix* L. leaves and the possible mechanism of action. Pak. J. Bot, 2004. 35(5; SPI): p. 805-810.

[86] Inayatullah, S., R. Irum, R. Ateeq ur, M. Fayyaz Chaudhary, and B. Mirza, Biological Evaluation of Some Selected Plant Species of Pakistan. Pharm. Biol, 2007. 45(5): p. 397-403. DOI: https://doi.org/10.1080/13880200701215182.

[87] Inayatullah, S., P.D. Prenzler, H.K. Obied, A. Rehman, and B. Mirza, Bioprospecting traditional Pakistani medicinal plants for potent antioxidants. Food Chemistry, 2012. 132(1): p. 222-229. DOI: https://doi.org/10.1016/j.foodchem.2011.10.060.

[88] Iskanderov, G.B., Oligosaccharides of *Hedera pastuchovii*. Chem. Nat. Compd, 1971. 7(4): p. 486-486. DOI: https://doi.org/10.1007/BF00564744.

[89] Jafri, L., S. Saleem, T.P. Kondrytuk, I. Haq, N. Ullah, J.M. Pezzuto, and B. Mirza, *Hedera nepalensis* K. Koch: A Novel Source of Natural Cancer Chemopreventive and Anticancerous Compounds. Phytother Res, 2016. 30(3): p. 447-453. DOI: https://doi.org/10.1002/ptr.5546.

[90] Jafri, L., S. Saleem, N. Ullah, and B. Mirza, *In vitro* assessment of antioxidant potential and determination of polyphenolic compounds of *Hedera nepalensis* K. Koch. Arab. J. Chem, 2017. 10: p. S3699-S3706. DOI: https://doi.org/10.1016/j.arabjc.2014.05.002.

[91] Jeong, H.G. and H.Y. Park, The prevention of carbon tetrachloride-induced hepatotoxicity in mice by *α*-hederin: Inhibiton of cytochrome P450 2E1 expression. IUBMB Life, 1998. 45(1): p. 163-170. DOI: https://doi.org/10.1080/15216549800202532.

[92] Kanwal, S., N. Ullah, I. Haq, I. Afzal, and B. Mirza, Antioxidant, antitumor activities and phytochemical investigation of *Hedera nepalensis* K. Koch, an important medicinal plant from Pakistan. Pak. J. Bot, 2011. 43(8): p. 85-9.

[93] Kemmerich, B., R. Eberhardt, and H. Stammer, Efficacy and tolerability of a fluid

extract combination of thyme herb and ivy leaves and matched placebo in adults suffering from acute bronchitis with productive cough. Arzneimittelforschung, 2006. 56(09): p. 652-660. DOI: https://doi.org/10.1055/s-0031-1296767.

[94] Khan, S., A. Adil, S. Naeem, N. Jaffar, H. Khatoon, H. Ansar, and Y. Shafiq, Evaluation of Acute and Chronic Antidiabetic Activity of Ivy (*Hedera helix* L.) Aqueous Leaf Extract in Rat Model. PJBS, 2020. 23(11): p. 1357-1368. DOI: https://doi.org/10.3923/pjbs.2020.1357.1368.

[95] Khdair, A., M.K. Mohammad, K. Tawaha, E. Al-Hamarsheh, H.S. AlKhatib, B. Al-Khalidi, Y. Bustanji, S. Najjar, and M. Hudaib, A validated RP HPLC-PAD method for the determination of hederacoside C in Ivy-Thyme cough syrup. International journal of analytical chemistry, 2010. 2010. DOI: https://doi.org/10.1155/2010/478143.

[96] Kim, D. and K. Kim, *Hedera rhombea* inhibits the biofilm formation of *Candida*, thereby increases the susceptibility to antifungal agent, and reduces infection. PloS one, 2021. 16(10): p. e0258108. DOI: https://doi.org/10.1371/journal.pone.0258108.

[97] Kim, E.H., S. Baek, D. Shin, J. Lee, and J.L. Roh, Hederagenin induces apoptosis in cisplatin-resistant head and neck cancer cells by inhibiting the Nrf2-ARE antioxidant pathway. Oxid. Med. Cell. Longev, 2017. 2017.

[98] Kim, K.S., Y.H. Choi, I.R. Lee, B.M. Kwon, and S.H. Lee, A novel nortriterpene from *Hedera rhombea*. Archives of Pharmacal Research, 1997. 20(2): p. 191. DOI: https://doi.org/10.1007/BF02974009.

[99] Kim, K.S., J.Y. Song, and R.L. Ihn, Protective Effects of the Phenolic Compounds from the Leaves of *Hedera rhombea* on Hepatic Injury. J. Pharm. Pharmacol, 1999. 43(4): p. 516-525.

[100] Kizu, H., S. Hirabayashi, M. Suzuki, and T. Tomimori, Studies on the constituents of *Hedera rhombea* Bean. IV. On the hederagenin glycosides.(2). Chem. Pharm. Bull, 1985. 33(8): p. 3473-3478. DOI: https://doi.org/10.1248/cpb.33.3473.

[101] Kizu, H., Y. Kikuchi, T. Tomimori, and T. Namba, Studies on the Nepalese Crude Drugs-4-On the Saponins in the Leaves of *Hedera nepalensis* K. Koch. Journal of Pharmacognosiculture, 1985. 39(2): p. p170-172.

[102] Kizu, H., S. Kitayama, F. Nakatani, T. Tomimori, and T. Namba, Studies on Nepalese Crude Drugs. III. On the Saponins of *Hedera nepalensis* K. KOCH. Chem. Pharm. Bull, 1985. 33(8): p. 3324-3329. DOI: https://doi.org/10.1248/cpb.33.3324.

[103] Kizu, H., M. Koshijima, M. Hayashi, and T. Tomimori, Studies on the constituents of *Hedera rhombea* Bean. II. On the dammarane triterpene glycosides.(1). Chem. Pharm. Bull, 1985. 33(4): p. 1400-1406. DOI: https://doi.org/10.1248/cpb.33.1400.

[104] Kizu, H., M. Koshijima, and T. Tomimori, Studies on the Constituents of *Hedera rhombea* BEAN. III. On the Dammarane Triterpene Glycosides. (2). Chem. Pharm. Bull, 1985. 33(8): p. 3176-3181. DOI: https://doi.org/10.1248/cpb.33.3176.

[105] Krivorutchenko, Y.L., D.N. Nosik, V.Y. Maligina, O.A. Lobach, I.B. Andronovskaja, M.A. Kirsanova, and V.I. Grishkovets, Cytotoxic Properties of Triterpene Saponin Taurosid SX1 and its Effect on Human Immunodefeciency Virus and Influenza Virus Infection in Mice. Problems of Virology, 2018. 63(3): p. 123-129. DOI: https://doi.org/10.18821/0507-4088-2018-63-3-123-129.

[106] Kurita, Y., P. Yamada, H. Shigemori, and H. Isoda, *Differentiation of Human Leukemia Cell Line HL-60 by a Polyacetylenic Compound from Hedera Rhombea*, in *Proceedings of the 19th Annual Meeting of the Japanese Association for Animal Cell Technology* 2009, Springer Netherlands: Japan. p. 253-258. DOI: https://doi.org/10.1007/978-1-4020-9646-4_39.

[107] Kwon, B.M., S.H. Lee, K.S. Kim, I.R. Lee, U.C. Lee, S.H. Hong, and S.H. Bok, Rhombenone: farnesyl protein transferase inhibitor from the leaves of *Hedera rhombea* Bean. Bioorganic & Medicinal Chemistry Letters, 1997. 7(8): p. 971-974. DOI: https://doi.org/10.1016/S0960-894X(97)00139-X.

[108] Lang, C., P. Röttger-Lüer, and C. Staiger, A valuable option for the treatment of respiratory diseases: review on the clinical evidence of the ivy leaves dry extract EA 575®. Planta Med, 2015. 81(12/13): p. 968-974. DOI: https://doi.org/10.1055/s-0035-1545879.

[109] Lee, C.D., J.K. Lee, J.H. Jeong, E.S. Park, U.D. Sohn, J.H. Lee, J.W. Shin, and J.Y. Lee, Inhibitory effects of an extract mixture of ivy (*Hedera helix*) leaves and *Coptidis rhizoma* on ovalbumin-induced allergic lung inflammation by co-exposure to Asian sand

dust in mice. Yakhak Hoeji, 2018. 62(1): p. 21-29. DOI: https://doi.org/10.17480/psk.2018.62.1.21.

[110] Lee, I.R., J.S. Kim, and S.H. Lee, Pharmacological activities of leaves of *Hedera rhombea* Bean. Korean J. Pharmacogn, 1992. 23(1): p. 34-42.

[111] Lee, I.R., M.S. Lee, K.A. Choi, and E.K. Seo, Pharmacological activities and the constituents of the leaves of *Hedera rhombea* Bean (II): On the constituents of the leaves. Archives of Pharmacal Research, 1993. 16(4): p. 331-335. DOI: https://doi.org/10.1007/BF02977526.

[112] Li, T., H. Pan, Y. Feng, H. Li, and Y. Zhao, Bioactivity-guided isolation of anticancer constituents from *Hedera nepalensis* K. Koch. S. Afr. J. Bot, 2015. 100: p. 87-93. DOI: https://doi.org/10.1016/j.sajb.2015.05.011.

[113] Loloiko, A.A., V.I. Grishkovets, A.S. Shashkov, and V.Y. Chirva, Triterpene glycosides of *Hedera taurica.* II. The structure of taurosides B and C from leaves of Crimean ivy. Chem. Nat. Compd, 1988. 24(3): p. 320-323. DOI: https://doi.org/10.1007/BF00598578.

[114] Loloiko, A.A., V.I. Grishkovets, A.S. Shashkov, and V.Y. Chirva, Triterpene glycosides of *Hedera taurica*. III. Structures of hederosides A3, B, E2 and F from the berries of Crimean ivy. Chem. Nat. Compd, 1988. 24(5): p. 614-618. DOI: https://doi.org/10.1007/BF00633392.

[115] Loloiko, A.A., V.I. Grishkovets, A.S. Shashkov, and V.Y. Chirva, Triterpene glycosides of *Hedera taurica*. IV. Structure of hederosides A1, A2, D1, and D2 from the berries of Crimean ivy. Chem. Nat. Compd, 1990. 26(2): p. 184-186. DOI: https://doi.org/10.1007/BF00607539.

[116] Lutsenko, Y., W. Bylka, I. Matlawska, and R. Darmohray, *Hedera helix* as a medicinal plant. Herba polonica, 2010. 56(1): p. 83-96.

[117] Lutsenko, Y., W. Bylka, I. Matławska, O. Gavrylyuk, M. Dworacka, A. Krawczyk, and V. Brytska, Anti-inflammatory, antimicrobial activity and influence on the lungs and bronchus of *Hedera helix* leaves extracts. Acta Pol. Pharm, 2017. 74(4): p. 1159-1166.

[118] Maffei Facino, R., M. Carini, and P. Bonadeo, Efficacy of topically applied *Hedera helix* L. saponins for treatment of liposclerosis so-called cellulitis. Acta therapeutica, 1990. 16(4): p. 337-349.

[119] Majester-Savornin, B., R. Elias, A.M. Diaz-Lanza, G. Balansard, M. Gasquet, and F. Delmas, Saponins of the ivy plant, *Hedera helix*, and their leishmanicidic activity. Planta Med, 1991. 57(03): p. 260-262. DOI: https://doi.org/10.1055/s-2006-960086.

[120] Medeiros, J.M.R., M. Macedo, J.P. Contancia, C. Nguyen, G. Cunningham, and D.H. Miles, Antithrombin activity of medicinal plants of the Azores. J. Ethnopharmacol, 2000. 72(1-2): p. 157-165. DOI: https://doi.org/10.1016/S0378-8741(00)00226-9.

[121] Medeiros, J.R., H. Medeiros, C. Mascarenhas, L.B. Davin, and N.G. Lewis, Bioactive components of *Hedera helix*. Arquipélago, Life and Marine Sciences, 2002. 19A: p. 27-32.

[122] Mel'nichenko, E.G., M.A. Kirsanova, V.I. Grishkovets, L.V. Tyshkevich, and K. IuL, Antimicrobial activity of saponins from *Hedera taurica* C ar r. Mikrobiolohichnyi Zhurnal (Kiev, Ukraine: 1993), 2003. 65(5): p. 8-12. DOI: https://doi.org/10.19082/1943.

[123] Mendel, M., M. Chłopecka, N. Dziekan, W. Karlik, and M. Wiechetek, Participation of extracellular calcium in α-hederin-induced contractions of rat isolated stomach strips. J. Ethnopharmacol, 2013. 146(1): p. 423-426. DOI: https://doi.org/10.1016/j.jep.2012.12.023.

[124] Mendel, M., M. Chłopecka, N. Dziekan, and M. Wiechetek, The effect of the whole extract of common ivy (*Hedera helix*) leaves and selected active substances on the motoric activity of rat isolated stomach strips. J. Ethnopharmacol, 2011. 134(3): p. 796-802. DOI: https://doi.org/10.1016/j.jep.2011.01.036.

[125] Meng, X. and Z. Wang, The volatile constituents analysis of *Scindapsus aureum* and *Hedera nepalensis* var. sinensis and their inhibition against five fungi. Acta Hortic, 2010. 37(6): p. 971-976.

[126] Moshaie-Nezhad, P., F. Faed Maleki, S.M. Hosseini, M. Yahyapour, M. Iman, and A. Khamesipour, Hepatoprotective and antioxidant effects of *Hedera helix* extract on acetaminophen induced oxidative stress and hepatotoxicity in mice. Biotechnic & Histochemistry, 2019. 94(5): p. 313-319. DOI: https://doi.org/10.1080/10520295.2019.1566569.

[127] Moshaie-Nezhad, P., S.M. Hosseini, M. Yahyapour, M. Iman, and A. Khamesipoure, Protective effect of ivy leaf extract on paracetamol-induced oxidative stress and nephrotoxicity in mice. J. HerbMed Pharmacol, 2019. 8(1). DOI: https://doi.org/10.15171/jhp.2019.11.

[128] Mot, A.C., C. Bischin, B. Muresan, M. Parvu, G. Damian, L. Vlase, and R. Silaghi-Dumitrescu, Antioxidant activity evaluation by physiologically relevant assays based on haemoglobin peroxidase activity and cytochrome c-induced oxidation of liposomes. Nat. Prod. Res, 2016. 30(11): p. 1315-1319. DOI: https://doi.org/10.1080/14786419.2015.1054824.

[129] Motaghi, S., M. Sadeghi, S. Seyyedin, G. Sepehri, and R. Kheirandish, Histomorphometrical and Histopathological Evaluation of *Hedera Helix* Alcoholic Extract on Dermal Collagen Bundles. Anat. Sci. Int, 2018. 15(2): p. 55-62.

[130] Moulin-Traffort, J., A. Favel, R. Elias, and P. Regli, Study of the action of *α*-hederin on the ultrastructure of *Candida albicans*: Untersuchungen zur Wirkung von α-Hederin auf die Ultrastruktur von *Candida albicans*. Mycoses, 1998. 41(9-10): p. 411-416. DOI: https://doi.org/10.1111/j.1439-0507.1998.tb00362.x.

[131] Mshvildadze, V., R. Elias, R. Faure, L. Debrauwer, G. Dekanosidze, E. Kemertelidze, and G. Balansard, Triterpenoid Saponins from Berries of *Hedera colchica*. Chem. Pharm. Bull, 2001. 49(6): p. 752-754. DOI: https://doi.org/10.1248/cpb.49.752.

[132] Mshvildadze, V., R. Elias, R. Faure, D. Rondeau, L. Debrauwer, G. Dekanosidze, E. Kemertelidze, and G. Balansard, Triterpenoid Saponins from Leaves of *Hedera pastuchowii*. Chem. Pharm. Bull, 2004. 52(12): p. 1411-1415. DOI: https://doi.org/10.1248/cpb.52.1411.

[133] Mshvildadze, V., O. Kunert, G. Dekanosidze, E. Kemertelidze, and E. Haslinger, Arjunolic acid derivative glycoside from the stems of *Hedera colchica*. Chem. Nat. Compd, 2005. 41(1): p. 48-51. DOI: https://doi.org/10.1007/s10600-005-0036-8.

[134] Mshvildadze, V.D., G.E. Dekanosidze, and E.P. Kemertelidze, Minor glycosides of *Hedera colchica*. Chem. Nat. Compd, 1992. 28(5): p. 516-516. DOI: https://doi.org/10.1007/BF00630674.

[135] Mulkijanyan, K., Z. Novikova, M. Sulakvelidze, M. Getia, V. Mshvildadze, and G. Dekanosidze, Ivy water extracts as gastric ulcer preventive agents. Georgian Medical News, 2013(224): p. 63-66.

[136] Nanyoung, K., S. Young June, P. SeonJu, Y. Guijae, K. YoonJae, Y. Hye Hyun, and K. Seung Hyun, Simultaneous determination of six compounds in *Hedera helix* L. using UPLC-ESI–MS/MS. Chromatographia, 2017. 80(7): p. 1025-1033. DOI: https://doi.org/10.1007/s10337-017-3317-z.

[137] Parvu, M., L. Vlase, A.E. Parvu, O. Rosca-Casian, A.M. Gheldiu, and O. Parvu, Phenolic compounds and antifungal activity of *Hedera helix* L.(Ivy) flowers and fruits. Notulae Botanicae Horti Agrobotanici Cluj-Napoca, 2015. 43(1): p. 53-58. DOI: https://doi.org/10.15835/nbha4319644.

[138] Pop, C.E., M. Parvu, A.L. Arsene, A.E. Parvu, D.C. Vodnar, M. Tarcea, A.M. Toiu, and L. Vlase, Investigation of antioxidant and antimicrobial potential of some extracts from *Hedera helix* L. Gut, 2017. 4(6): p. 11.

[139] Prescott, T.A.K., L.P. Rigby, N.C. Veitch, and M.S.J. Simmonds, The haploinsufficiency profile of *α*-hederin suggests a caspofungin-like antifungal mode of action. Phytochemistry, 2014. 101: p. 116-120. DOI: https://doi.org/10.1016/j.phytochem.2014.01.022.

[140] Quetin-Leclercq, J., R. Elias, G. Balansard, R. Bassleer, and L. Angenot, Cytotoxic activity of some triterpenoid saponins. Planta Med, 1992. 58(03): p. 279-281. DOI: https://doi.org/10.1055/s-2006-961456.

[141] Rai, A., The antiinflammatory and antiarthritic properties of ethanol extract of *Hedera helix*. Indian J. Pharm. Sci, 2013. 75(1): p. 99. DOI: https://doi.org/10.4103/0250-474X.113537.

[142] Rauf, A., G. Uddin, H. Khan, B.S. Siddiqui, M. Arfan, M. Yousuf, and A. Hussain, Analgesic and Antioxidant Activity of Crude Extracts and Isolated Fractions of Aerial Parts of *Hedera helix* L. . JSM Chemistry 2014. 2(2): p. 1-5.

[143] Rehman, K.U., M. Hamayun, T. Yaseen, Z.A. Butt, G. Ahmad, and S. Wali, The Usefulness of Common IVY (*Hedera helix* L.) Extracts Against Bacterial and Fungal Pathogens Found in Local Hospitals: Uses of *Hedera helix* L. for Bacterial and Fungal Disease. Biological Sciences-PJSIR, 2022. 65(1): p. 45-49. DOI: https://doi.org/10.52763/PJSIR.BIOL.SCI.65.1.2022.45.49.

[144] Ridoux, O., C. Di Giorgio, F. Delmas, R. Elias, V. Mshvildadze, G.E. Dekanosidze, E. Kemertelidze, G. Balansard, and P. Timon-David, *In vitro* antileishmanial activity of three saponins isolated from ivy, *α*-hederin, *β*-hederin and hederacolchiside A1, in association with pentamidine and amphotericin B. Phytother Res, 2001. 15(4):

p. 298-301. DOI: https://doi.org/10.1002/ptr.723.

[145] Romman, M., *Comparative Pharmacological and Biological Evaluation of the Stem and Leaves of Hedera nepalensis from District Malakand Khyber Pakhtunkhwa, Pakistan*. 2016, ISLAMIA COLLEGE PESHAWAR KHYBER PAKHTUNKHWA: Pakistan.

[146] Romman, M., S. Jan, M. Hamayun, I. Ahmad, and S. Wali, *In vitro* Antioxidant activity of stem and leaves extracts of *Hedera nepalensis* K. Koch. Int. J. Biosci, 2015. 7: p. 19-24.

[147] Roşca-Casian, O., C. Mircea, L. Vlase, A.M. Gheldiu, D.T. Teuca, and M. Pârvu, Chemical composition and antifungal activity of *Hedera helix* leaf ethanolic extract. Acta Biologica Hungarica, 2017. 68(2): p. 196-207. DOI: https://doi.org/10.1556/018.68.2017.2.7.

[148] Rothan, H.A. and S.N. Byrareddy, The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J. Autoimmun, 2020. 109: p. 102433. DOI: https://doi.org/10.1016/j.jaut.2020.102433.

[149] Saiah, H., R. Allem, and Z. El Kebir, Antioxidant and antibacterial activities of six Algerian medicinal plants. Int. J. Pharm. Pharm. Sci, 2016. 8(1): p. 367-374.

[150] Saleem, S., L. Jafri, I. ul Haq, L.C. Chang, D. Calderwood, B.D. Green, and B. Mirza, Plants *Fagonia cretica* L. and *Hedera nepalensis* K. Koch contain natural compounds with potent dipeptidyl peptidase-4 (DPP-4) inhibitory activity. J. Ethnopharmacol, 2014. 156: p. 26-32. DOI: https://doi.org/10.1016/j.jep.2014.08.017.

[151] Sales-Medina, D.F., L.R.P. Ferreira, L.M.D. Romera, K.R. Gonçalves, R.V.C. Guido, G. Courtemanche, M.S. Buckeridge, É.L. Durigon, C.B. Moraes, and L.H. Freitas-Junior, Discovery of clinically approved drugs capable of inhibiting SARS-CoV-2 in vitro infection using a phenotypic screening strategy and network-analysis to predict their potential to treat covid-19. BioRxiv, 2020. DOI: https://doi.org/10.1101/2020.07.09.196337.

[152] Salma, U., T. Khan, and A. Shah, Antihypertensive efficacy of extract of *Hedera helix* in high salt-induced hypertensive Sprague-Dawley rats. Asian Pac. J. Trop. Med, 2018. 11(8): p. 473. DOI: https://doi.org/10.4103/1995-7645.240083.

[153] Sareedenchai, V. and C. Zidorn, Sequestration of polyacetylenes by the parasite *Orobanche hederae* (Orobanchaceae) from its host *Hedera helix* (Araliaceae). Biochemical Systematics and Ecology, 2008. 36(10): p. 772-776. DOI: https://doi.org/10.1016/j.bse.2008.09.002.

[154] Schulte-Michels, J., F. Runkel, S. Gokorsch, and H. Häberlein, Ivy leaves dry extract EA 575® decreases LPS-induced IL-6 release from murine macrophages. Die Pharmazie-An International Journal of Pharmaceutical Sciences, 2016. 71(3): p. 158-161. DOI: https://doi.org/10.1691/ph.2016.5835.

[155] Shah, A., M.S.S. Khan, M. Ahmad, and H. Sher, Voltage-dependent ca2+ entry blocking activity of *Hedera helix* leaf extract explains its medicinal use in hyperactive gut disorders FARMACIA, 2018. 66(1): p. 115-119.

[156] Shashkov, A.A., V.I. Grishkovets, O.Y. Tsvetkov, and V.Y. Chirva, Triterpene glycosides of *Hedera taurica*. XI. Structures of taurosides St-G 1, St-H 1, and St-H 2 from the stems of Crimean ivy. Chem. Nat. Compd, 1993. 29(4): p. 502-508. DOI: https://doi.org/10.1007/BF00630578.

[157] Shashkov, A.S., V.I. Grishkovets, A.E. Kondratenko, and V.Y. Chirva, Triterpene glycosides of *Hedera helix* II. Determination of the structure of glycoside L-6d from common ivy leaves. Chem. Nat. Compd, 1994. 30(6): p. 693-698. DOI: https://doi.org/10.1007/BF00630605.

[158] Shashkov, A.S., V.I. Grishkovets, A.A. Loloiko, and V.Y. Chirva, Triterpene glycosides of *Hedera taurica* I. Structure of tauroside E from the leaves of *Hedera taurica*. Chem. Nat. Compd, 1987. 23(3): p. 299-302. DOI: https://doi.org/10.1007/BF00600827.

[159] Shashkov, A.S., V.I. Grishkovets, L.A. Yakovishin, I.N. Shchipanova, and V.Y. Chirva, Triterpene glycosides of *Hedera canariensis* II. Determination of the structures of glycosides LE 2 and LH 3 from the leaves of Algerian ivy. Chem. Nat. Compd, 1998. 34(6): p. 690-693. DOI: https://doi.org/10.1007/BF02336095.

[160] Shawky, E. and S.M. El Sohafy, Untargeted and targeted chemical profiling for efficacy-directed discrimination of *Hedera helix* L. subspecies using HPTLC-image analysis and HPTLC/MS. Ind Crops Prod, 2020. 145: p. 111980. DOI: https://doi.org/10.1016/j.indcrop.2019.111980 .

[161] Shimizu, M., M. Arisawa, N. Morita, K. Kizu, and T. Tomimori, Studies on the constituents of *Hedera rhombea* Bean. I. Glycosides of hederagenin. Chem. Pharm. Bull, 1978. 26(2): p. 655-659. DOI: https://doi.org/10.1248/cpb.26.655.

[162] Shokry, A.A., R.A. El-Shiekh, G. Kamel, A.F. Bakr, and A. Ramadan, Bioactive phenolics fraction of *Hedera helix* L.(Common Ivy Leaf) standardized extract ameliorates LPS-induced acute lung injury in the mouse model through the inhibition of proinflammatory cytokines and oxidative stress. Heliyon, 2022: p. e09477. DOI: https://doi.org/10.1016/j.heliyon.2022.e09477.

[163] Shokry, A.A., R.A. El-Shiekh, G. Kamel, A.F. Bakr, D. Sabry, and A. Ramadan, Anti-arthritic activity of the flavonoids fraction of ivy leaves (*Hedera helix* L.) standardized extract in adjuvant induced arthritis model in rats in relation to its metabolite profile using LC/MS. Biomedicine & Pharmacotherapy, 2022. 145: p. 112456. DOI: https://doi.org/10.1016/j.biopha.2021.112456.

[164] Sieben, A., L. Prenner, T. Sorkalla, A. Wolf, D. Jakobs, F. Runkel, and H. Häberlein, *α*-Hederin, but not hederacoside C and hederagenin from *Hedera helix,* affects the binding behavior, dynamics, and regulation of *β*2-adrenergic receptors. Biochemistry, 2009. 48(15): p. 3477-3482. DOI: https://doi.org/10.1021/bi802036b.

[165] Sierocinski, E., F. Holzinger, and J.F. Chenot, Ivy leaf (*Hedera helix*) for acute upper respiratory tract infections: an updated systematic review. Eur. J. Clin. Pharmacol, 2021. 77(8): p. 1113-1122. DOI: https://doi.org/10.1007/s00228-021-03090-4.

[166] Silveira, D., J.M. Prieto-Garcia, F. Boylan, O. Estrada, Y.M. Fonseca-Bazzo, C.M. Jamal, P.O. Magalhães, E.O. Pereira, M. Tomczyk, and M. Heinrich, COVID-19: Is There Evidence for the Use of Herbal Medicines as Adjuvant Symptomatic Therapy? Frontiers in Pharmacology, 2020. 11. DOI: https://doi.org/10.3389/fphar.2020.581840.

[167] Small, E., 58. Ivy (*Hedera* species)–virtues and vices of the world's most popular ornamental vine. Biodiversity, 2019. 20(1): p. 62-74. DOI: https://doi.org/10.1080/14888386.2018.1524790.

[168] So Ri, K., L. Yong Chul, C.h. Yeong Hun, and J. Jae Seok, OP-108: The herbal extract mixture of *Hedera helix* and *Coptidis rhizoma* attenuates both eosinophilic and neutrophilic severe asthmatic features in mice. Korean Tuberculosis and Respiratory Society, 2019. 127: p. 393-393.

[169] Song, J., S. Yeo, E. Hong, B. Lee, J. Kim, J. Kim, H. Jeong, Y. Kwon, H. Kim, S. Lee, J. Park, and H. Ko, Antiviral Activity of Hederasaponin B from *Hedera helix* against Enterovirus 71 Subgenotypes C3 and C4a. Biomol Ther, 2014. 22(1): p. 41-46. DOI: https://doi.org/10.4062/biomolther.2013.108.

[170] Song, K.J., Y.J. Shin, K.R. Lee, E.J. Lee, Y.S. Suh, and K. Kyung-Su, Expectorant and antitussive effect of *Hedera helix* and *Rhizoma coptidis* extracts mixture. Yonsei Med. J, 2015. 56(3): p. 819-824. DOI: https://doi.org/10.3349/ymj.2015.56.3.819.

[171] Stauss-Grabo, M., S. Atiye, A. Warnke, R.S. Wedemeyer, F. Donath, and H.H. Blume, Observational study on the tolerability and safety of film-coated tablets containing ivy extract (Prospan® Cough Tablets) in the treatment of colds accompanied by coughing. Phytomedicine, 2011. 18(6): p. 433-436. DOI: https://doi.org/10.1016/j.phymed.2010.11.009.

[172] Süleyman, H., V. Mshvildadze, A. Gepdiremen, and R. Elias, Acute and chronic antiinflammatory profile of the ivy plant, *Hedera helix*, in rats. Phytomedicine, 2003. 10(5): p. 370-374. DOI: https://doi.org/10.1078/0944-7113-00260.

[173] Tatia, R., T. A., L. Moldovan, C. Zălaru, and I. Călinescu, Phytochemical and antiproliferative potential of *Hedera helix* extract fractions. UPB Sci. Bull. B: Chem. Mater, 2020.

[174] Tatia, R., C. Zalaru, O. Craciunescu, L. Moldovan, A. Oancea, and I. Calinescu, Optimization of triterpene saponins mixture with antiproliferative activity. Appl. Sci, 2019. 9(23): p. 5160. DOI: https://doi.org/10.3390/app9235160.

[175] Tedlaouti, F., M. Gasquet, F. Delmas, P. Timon-David, R. Elias, E. Vidal-Ollivier, F. Crespin, and G. Balansard, Antitrypanosomial Activity of Some Saponins from *Calendula arvensis*, *Hedera helix*, and *Sapindus mukurossi*. Planta Med, 1991. 57(S 2): p. A78-A78. DOI: https://doi.org/10.1055/s-2006-960347.

[176] Thi Thuy, D., H. Thanh , N. Tuan , P. Thanh , N. Minh , and D. Doan Simultaneous Quantification of Hederacoside C and α-hederin in *Hedera Nepalensis* K.Koch Using HPLC-UV. VNU Journal of Science: Medical and Pharmaceutical Sciences, 2020. 36(3). DOI: https://doi.org/10.25073/2588-1132/vnumps.4227.

[177] Tomimori, T., Y. Kikuchi, Y. Imoto, and H. Kizu, On Saponins from *Hedera rhombea* Bean var. formosana Li. Journal of

Pharmacognosiculture, 1987. 41(1): p. p55-57.

[178] Tong, X., X. Chen, X. Jiang, and J. Yu, Extraction and GC-MS Analysis of Volatile Oil from *Hedera nepalensis* var. sinensis [J]. Fine Chemicals, 2007. 6.

[179] Trute, A., J. Gross, E. Mutschler, and A. Nahrstedt, *In vitro* antispasmodic compounds of the dry extract obtained from *Hedera helix*. Planta Med, 1997. 63(02): p. 125-129. DOI: https://doi.org/10.1055/s-2006-957627.

[180] Trute, A., J. Gross, E. Mutschler, and A. Nahrstedt, In Vitro Antispasmodic Compounds of the Dry Extract Obtained from *Hedera helix*. Planta Med, 1997. 63(02): p. 125-129. DOI: 10.1055/s-2006-957627.

[181] Trute, A. and A. Nahrstedt, Identification and quantitative analysis of phenolic compounds from the dry extract of *Hedera helix*. Planta Med, 1997. 63(02): p. 177-179. DOI: https://doi.org/10.1055/s-2006-957639.

[182] Tsolmon, S., Y. Kurita, P. Yamada, H. Shigemori, and H. Isoda, Indoleacetic acid falcarindiol ester induces granulocytic differentiation of the human leukemia cell line HL-60. Planta Med, 2009. 75(01): p. 49-54. DOI: https://doi.org/10.1055/s-0028-1088370.

[183] Tucker, A.O. and M.J. Maciarello, Essential Oil of English Ivy, *Hedera helix* L. 'Hibernica'. J. Essent, 1994. 6(2): p. 187-188. DOI: https://doi.org/10.1080/10412905.1994.9698352.

[184] Uddin, G., A. Khan, M. Alamzeb, S. Ali, M. Alam, A. Rauf, and W. Ullah, Biological screening of ethyl acetate extract of *Hedera nepalensis* stem. Afr. j. pharm. pharmacol, 2012. 6(42): p. 2934-2937. DOI: https://doi.org/10.5897/AJPP12.828.

[185] Uddin, G., A. Rauf, M. Qaisar, A. Latif, and M. Ali, Preliminary phytochemical screening and antimicrobial activity of *Hedera helix* L. Middle East J. Sci. Res, 2011. 8(1): p. 198-202.

[186] Ullah, S., M.A. Abbasi, M.A. Raza, S.U. Khan, B.M. Aziz-ur-Rehman, and M. Mughal, Antibacterial activity of some selected plants of Swat valley. Biosci, 2011. 8(1): p. 15-18.

[187] Villani, P., T. Orsiere, I. Sari-Minodier, G. Bouvenot, and A. Botta. *In vitro study of the antimutagenic activity of alpha-hederin*. in *Annales de Biologie Clinique*. 2001.

[188] Woldemichael, T., A. Debella, D. Abebe, G. Tassew, T. Biru, Y. Makonnen, F. Teka, and D. Melaku, Screening OF Some Medicinal Plants OF Ethiopia For Their Molluscicidal Activities and Phytochemical Constituents. Pharmacology Online, 2006. 3: p. 245-258. DOI: https://doi.org/10.1016/j.jep.2004.08.021.

[189] Wolf, A., R. Gosens, H. Meurs, and H. Häberlein, Pre-treatment with α-hederin increases β-adrenoceptor mediated relaxation of airway smooth muscle. Phytomedicine, 2011. 18(2-3): p. 214-218. DOI: https://doi.org/10.1016/j.phymed.2010.05.010.

[190] Yakovishin, L.A., D.Y. Belash, and I.R. Yarovoy, Molecular complex of the triterpene glycoside α-hederin and sildenafil citrate (viagra): FT-IR and UV spectroscopy analysis and biological activity. Ukr, 2012. 10(1): p. 38-41.

[191] Yakovishin, L.A., V.A. Ertahova, E.A. Bazyura, Л.О. Яковішин, В.А. Єртахова, and К.А. Базюра, Influence of the triterpene glycosides and their complexes on mollusks. . Ukr, 2006. 4(2): p. 22-26.

[192] Yakovishin, L.A., V.I. Grishkovets, N.N. Arnautov, and V.Y. Chirva, Triterpene glycosides of *Hedera canariensis*. V. Structure of glycosides from canary ivy stems. Chem. Nat. Compd, 1999. 35(5): p. 587-588. DOI: https://doi.org/10.1007/BF02323306.

[193] Yakovishin, L.A., V.I. Grishkovets, A.S. Shashkov, and V.Y. Chirva, Triterpene glycosides from *Hedera canariensis* VI. Structure of L-G1 and L-G1b glycosides from leaves of canary ivy. Chem. Nat. Compd, 1999. 35(5): p. 543-546. DOI: https://doi.org/10.1007/BF02323291.

[194] Yakovishin, L.A., V.I. Grishkovets, I.N. Shchipanova, A.S. Shashkov, and V.Y. Chirva, Triterpene glycosides of *Hedera canariensis* IV. Structures of glycosides LF_3, LG_0, and LG_{1a} from the leaves of Algerian ivy. Chem. Nat. Compd, 1999. 35(1): p. 65-69.

[195] Yakovishin, L.A., V.I. Grishkovets, and N.V. Tolkacheva, Triterpene glycosides of *Hedera canariensis*. VII. Structures of glycosides from roots of canary ivy. Chem. Nat. Compd, 2001. 37(6): p. 573-574. DOI: https://doi.org/10.1023/A:1014837420539.

[196] Yamazoe, S., K. Hasegawa, J. Ito, Y. Mikami, and H. Shigemori, Hederyne A, a new antimicrobial polyacetylene from galls of *Hedera rhombea* Bean. J Asian Nat Prod Res, 2007. 9(6): p. 537-540. DOI: https://doi.org/10.1080/10286020600882379.

[197] Yamazoe, S., K. Hasegawa, and H. Shigemori, Structure-activity relationship of acetylenes from galls of *Hedera rhombea* as

plant growth inhibitors. Zeitschrift für Naturforschung C, 2006. 61(7-8): p. 536-540. DOI: https://doi.org/10.1515/znc-2006-7-811.

[198] Yamazoe, S., K. Hasegawa, and H. Shigemori, Growth inhibitory indole acetic acid polyacetylenic ester from Japanese ivy (*Hedera rhombea* Bean). Phytochemistry, 2007. 68(12): p. 1706-1711. DOI: https://doi.org/10.1016/j.phytochem.2007.03.036.

[199] Yamazoe, S., K. Hasegawa, K. Suenaga, and H. Shigemori, Growth inhibitory polyacetylenes from galls of *Hedera rhombea* Bean. Nat. Prod. Commun, 2006. 1(2): p. 1934578X0600100202. DOI: https://doi.org/10.1177%2F1934578X0600100202.

[200] Yang, L., Y. Xie, Z. Li, W. Li, M. He, B. Wu, Y. Feng, and S. Yang, Analysis of chemical constituents in *Hedera nepalensis* by UPLC/Q-TOF-MS/MS. Zhong Cao Yao, 2016: p. 566-572.

[201] Yokosuka, A., T. Shimomura, S. Yokogawa, A. Oguro, K. Miyake, and Y. Mimaki, Chemical Components in *Hedera rhombea* Leaves and Their Cytotoxicity. Chem. Pharm. Bull, 2022. 70(2): p. 175-181. DOI: https://doi.org/10.1248/cpb.c21-00907.

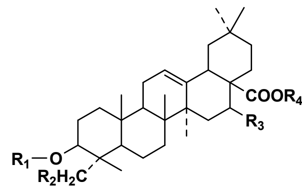
[202] Yu, M., Y.J. Shin, N. Kim, G. Yoo, S. Park, and S.H. Kim, Determination of saponins and flavonoids in ivy leaf extracts using HPLC-DAD. J. Chromatogr, 2015. 53(4): p. 478-483. DOI: https://doi.org/10.1093/chromsci/bmu068.

[203] Zazharskyi, V.V., P.O. Davydenko, O.M. Kulishenko, I.V. Borovik, and V.V. Brygadyrenko, Antibacterial and fungicidal activities of ethanol extracts from *Cotinus coggygria*, *Rhus typhina*, *R. trilobata*, *Toxicodendron orientale*, *Hedera helix*, *Aralia elata*, *Leptopus chinensis* and *Mahonia aquifolium*. Regulatory Mechanisms in Biosystems, 2020. 11(2): p. 305-309.

[204] Zeil, S., U. Schwanebeck, and C. Vogelberg, Tolerance and effect of an add-on treatment with a cough medicine containing ivy leaves dry extract on lung function in children with bronchial asthma. Phytomedicine, 2014. 21(10): p. 1216-1220. DOI: https://doi.org/10.1016/j.phymed.2014.05.006.

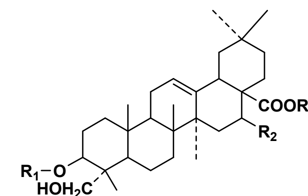
[205] Žugić, A., S. Đorđević, I. Arsić, G. Marković, J. Živković, S. Jovanović, and V. Tadić, Antioxidant activity and phenolic compounds in 10 selected herbs from Vrujci Spa, Serbia. Ind Crops Prod, 2014. 52: p. 519-527. DOI: https://doi.org/10.1016/j.indcrop.2013.11.027.

[206] Kirsanova, M.A., Y.L. Krivorutchenko, D.N. Nossik, and O.A. Lobach, *Study Of Cytotoxic And Antiproliferative Activity Of Fungicidal Saponin Taurosid Sx1 On Transformed Mammalian Cells*, in *Molecular bases of epidemiology, diagnostics, prevention and treatment of infectious diseases*. 2018: St. Petersburg. p. 614.

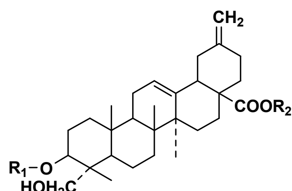


1 R_1= α–L-Ara$_p$, R_2= H, R_3=H, R_4=H
2 R_1= α–L-Ara$_p$, R_2= H, R_3=OH, R_4=H
3 R_1= α–L-Ara$_p$, R_2= OH, R_3=H, R_4=
4 R_1=α–L-Rha$_p$-(1-2)-α-L-Ara$_p$, R_2=H, R_3=H, R_4=H
5 R_1=α–L-Rha$_p$-(1-2)-α-L-Ara$_p$, R_2=H, R_3=OH, R_4=H
6 R_1=α–L-Rha$_p$-(1-2)-α-L-Ara$_p$, R_2=OH, R_3=H, R_4=H

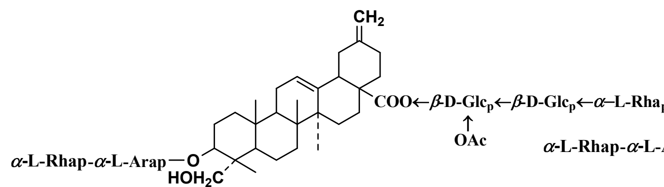
7 R_1=α–L-Ara$_p$, R_2=OH, R_3=H, R_4= β-D-Glc$_p$-(6-1)-β-D-Glc$_p$-(4-1)-α–L-Rha$_p$
8 R_1=α–L-Rha$_p$-(1-2)-α-L-Ara$_p$, R_2=H, R_3=H, R_4= β-D-Glc$_p$-(6-1)-β-D-Glc$_p$-(4-1)-α–L-Rha$_p$
9 R_1=α–L-Rha$_p$-(1-2)-α-L-Ara$_p$, R_2=OH, R_3=H, R_4= β-D-Glc$_p$-(6-1)-β-D-Glc$_p$
10 R_1=α–L-Rha$_p$-(1-2)-α-L-Ara$_p$, R_2=OH, R_3=H, R_4=H
↑
β-D-Glc$_p$-(6-1)-β-D-Glc$_p$-(4-1)-α–L-Rha$_p$
11 R_1=α–L-Rha$_p$-(1-2)-α-L-Ara$_p$, R_2=H, R_3=OH, R_4= β-D-Glc$_p$-(6-1)-β-D-Glc$_p$-(4-1)-α–L-Rha$_p$
12 R_1=α–L-Rha$_p$-(1-2)-α-L-Ara$_p$, R_2=OH, R_3=H, R_4= β-D-Glc$_p$-(6-1)-β-D-Glc$_p$-(4-1)-α–L-Rha$_p$
13 R_1=α–L-Rha$_p$-(1-2)-β-D-Glc$_p$, R_2=OH, R_3=H, R_4= β-D-Glc$_p$-(6-1)-β-D-Glc$_p$-(4-1)-α–L-Rha$_p$



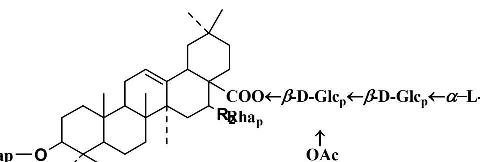
14 R_1=α-L-Rha$_p$-(1- 2)-β-D-Glc$_p$, R_2=H, R_3=H
15 R_1=α-L-Rha$_p$-(1- 2)-α-L-Ara$_p$, R_2=OH, R_3=H
16 R_1=α-L-Rha$_p$-(1- 2)-α-L-Ara$_p$, R_2=OH, R_3=β-D-Glc$_p$-(6-1)-β-D-Glc$_p$-(4-1)-α–L-Rha$_p$



17 R_1=α-L-Rha$_p$-(1- 2)-α-L-Ara$_p$, R_2=H
18 R_1=α-L-Rha$_p$-(1- 2)-α-L-Ara$_p$, R_2=β-D-Glc$_p$-(6-1)-β-D-Glc$_p$-(4-1)-α–L-Rha$_p$
19 R_1=α-L-Ara$_p$, R_2=β-D-Glc$_p$-(6-1)-β-D-Glc$_p$-(4-1)-α–L-Rha$_p$

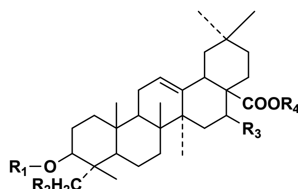


20

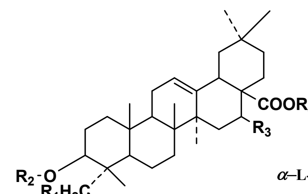


α-L-Rhap-α-L-Arap—O

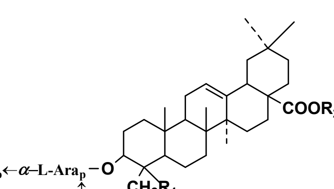
21 R_1=H, R_2=H
22 R_1=H, R_2=OH
23 R_1=OH, R_2=H



24 R_1=α-L-Ara$_p$, R_2=H, R_3= OH, R_4= β-D-Glc$_p$-(6-1)-β-D-Glcp-(4-1)-α-L-Rha$_p$
25 R_1= GlcUA$_p$β-, R_2=H, R_3= H, R_4= H
26 R_1= GlcUA$_p$β-, R_2=OH, R_3= H, R_4= H
27 R_1= GlcUA$_p$β-, R_2=H, R_3= H, R_4= β-D-Glc$_p$-(6 - 1)-β-D-Glcp-(4-1)-α-L-Rha$_p$
28 R_1= GlcUA$_p$β-, R_2=OH, R_3= H, R_4= β-D-Glc$_p$-(6 - 1)-β-D-Glcp-(4-1)-α-L-Rha$_p$
29 R_1= β-D-Glc$_p$-(1-2)-α-L-Ara$_p$, R_2=OH, R_3= H, R_4= β-D-Glc$_p$-(6-1)-β-D-Glcp-(4-1)-α-L-Rha$_p$



30 R_1=H, R_2=H, R_3= H, R_4= β-D-Glc$_p$-(6-1)-β-D-Glcp-(4-1)-α-L-Rha$_p$
31 R_1=α-L-Ara$_p$, R_2=H, R_3= H, R_4= β-D-Glc$_p$-(6-1)-β-D-Glcp-(4-1)-α-L-Rha$_p$
32 R_1=$SO_3^-H^+$, R_2=H, R_3= H, R_4=H
33 R_1=$SO_3^-H^+$, R_2=H, R_3=OH, R_4=H



34 R_1=H, R_2=H
35 R_1=OH, R_2=H
36 R_1=H, R_2=β-D-Glc$_p$-(6-1)-β-D-Glcp-(4-1)-α-L-Rha$_p$
37 R_1=OH, R_2=β-D-Glc$_p$-(6-1)-β-D-Glcp-(4-1)-α-L-Rha$_p$

α-L-Ara$_p$=α-L-Arabinopyranosyl, α-L-Rha$_p$=α-L-Rhamnopyranosyl, β-D-Glc$_p$= β-D-Glucopyranosyl, β-D-GlcUA$_p$= β-D-Glucuronopyranosyl

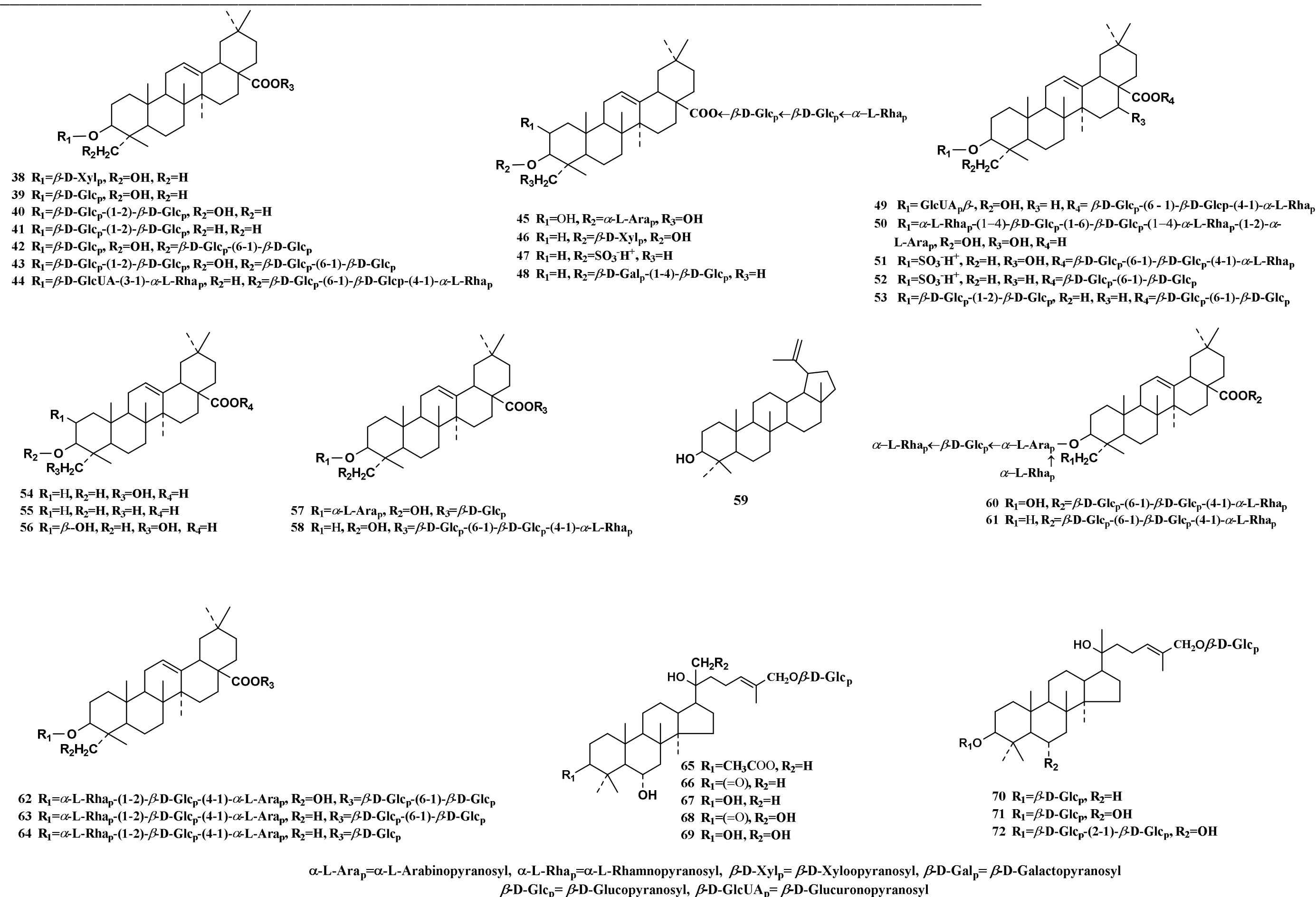


Fig. (2): Chemical structures of reported triterpene glycosides from Genus *Hedera* (Compounds 38-72)

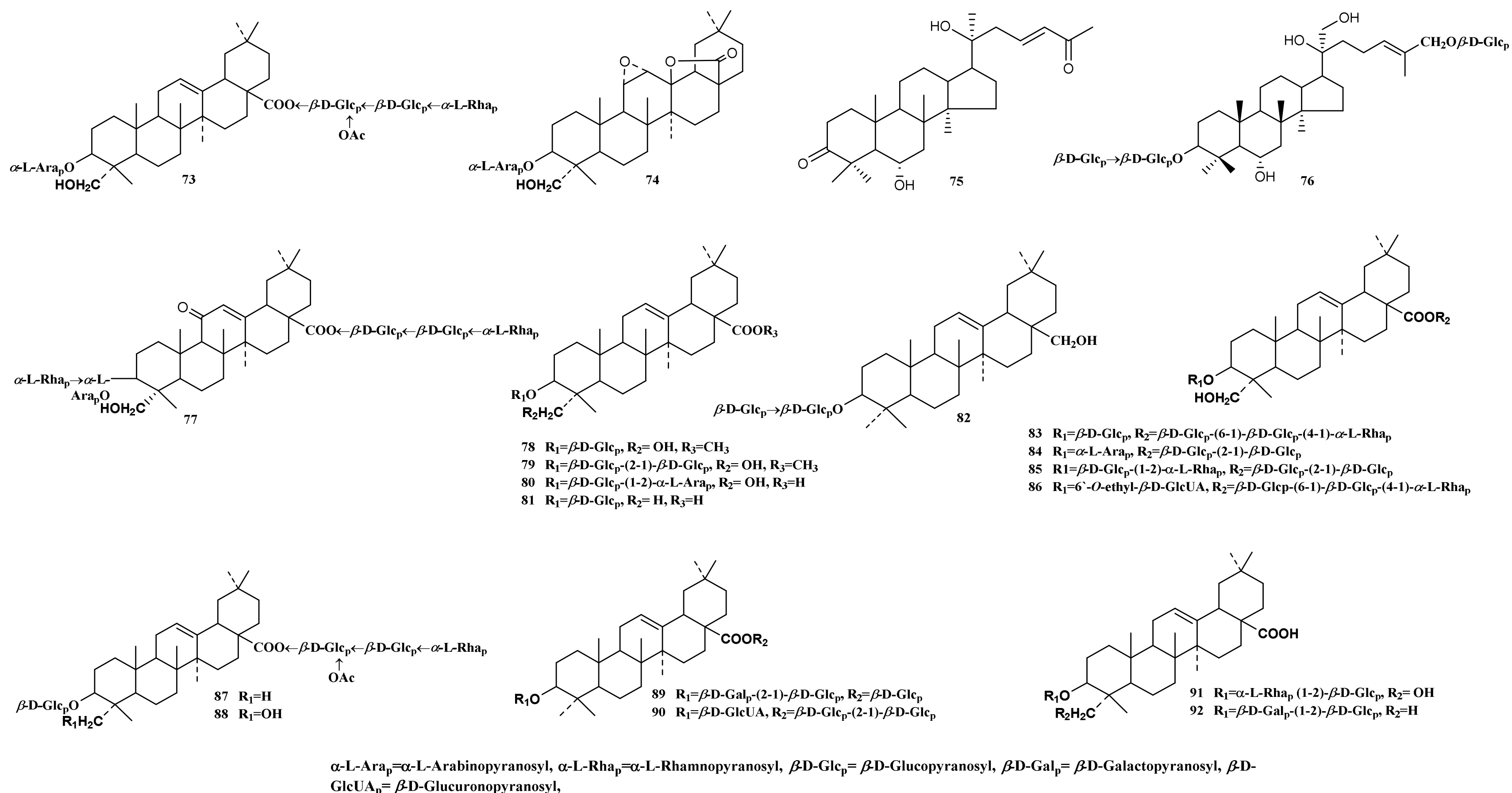
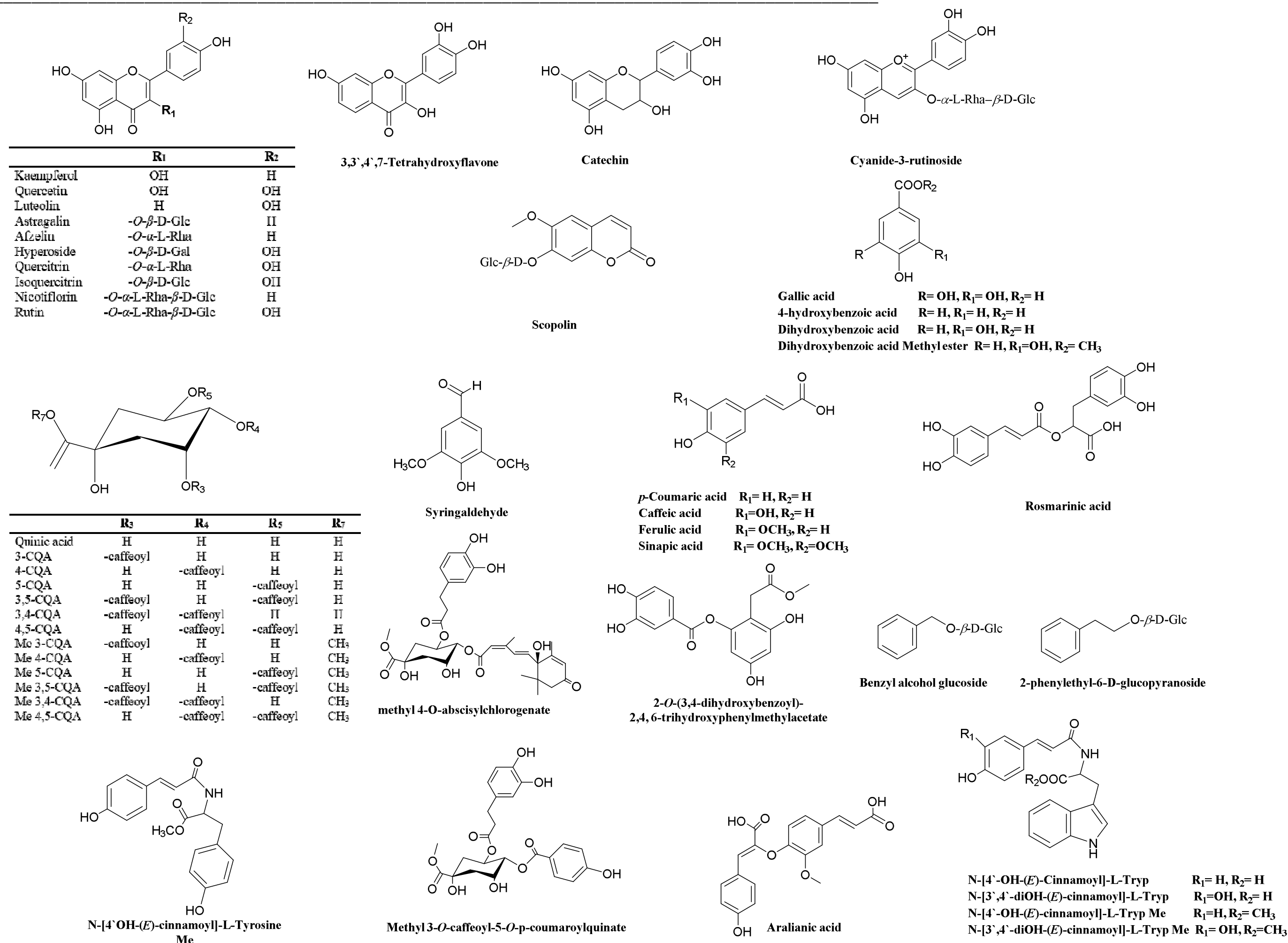


Fig. (3): Chemical structures of reported triterpene glycosides from Genus *Hedera* (Compounds 73-92)



	R1	R2
Kaempferol	OH	H
Quercetin	OH	OH
Luteolin	H	OH
Astragalin	-O-β-D-Glc	H
Afzelin	-O-α-L-Rha	H
Hyperoside	-O-β-D-Gal	OH
Quercitrin	-O-α-L-Rha	OH
Isoquercitrin	-O-β-D-Glc	OH
Nicotiflorin	-O-α-L-Rha-β-D-Glc	H
Rutin	-O-α-L-Rha-β-D-Glc	OH

	R3	R4	R5	R7
Quinic acid	H	H	H	H
3-CQA	-caffeoyl	H	H	H
4-CQA	H	-caffeoyl	H	H
5-CQA	H	H	-caffeoyl	H
3,5-CQA	-caffeoyl	H	-caffeoyl	H
3,4-CQA	-caffeoyl	-caffeoyl	H	H
4,5-CQA	H	-caffeoyl	-caffeoyl	H
Me 3-CQA	-caffeoyl	H	H	CH3
Me 4-CQA	H	-caffeoyl	H	CH3
Me 5-CQA	H	H	-caffeoyl	CH3
Me 3,5-CQA	-caffeoyl	H	-caffeoyl	CH3
Me 3,4-CQA	-caffeoyl	-caffeoyl	H	CH3
Me 4,5-CQA	H	-caffeoyl	-caffeoyl	CH3

Fig. (4): Chemical structures of reported phenolic constituents from Genus *Hedera*

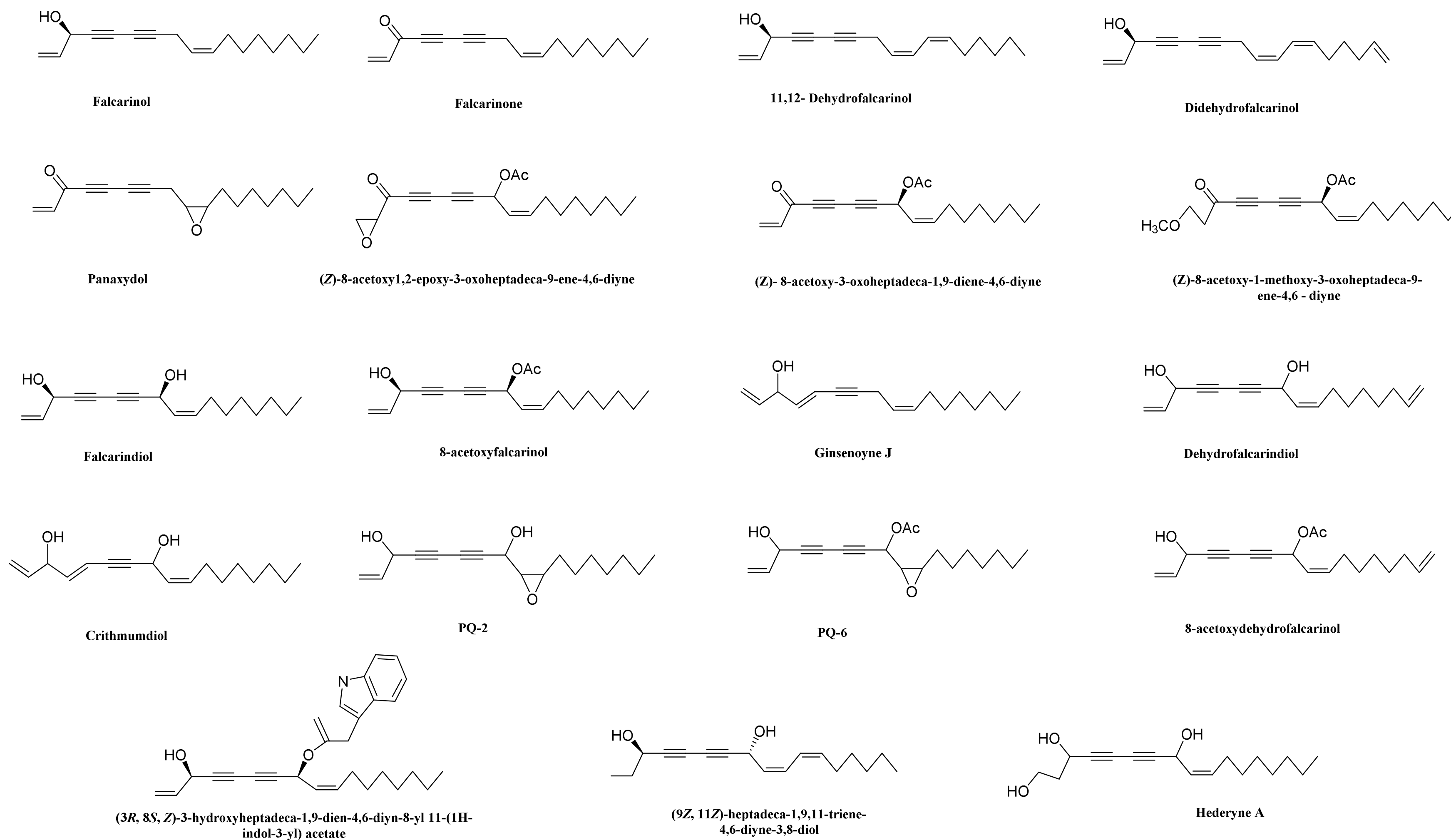


Fig. (5): Chemical structures of reported polyacetylenes from Genus *Hedera*

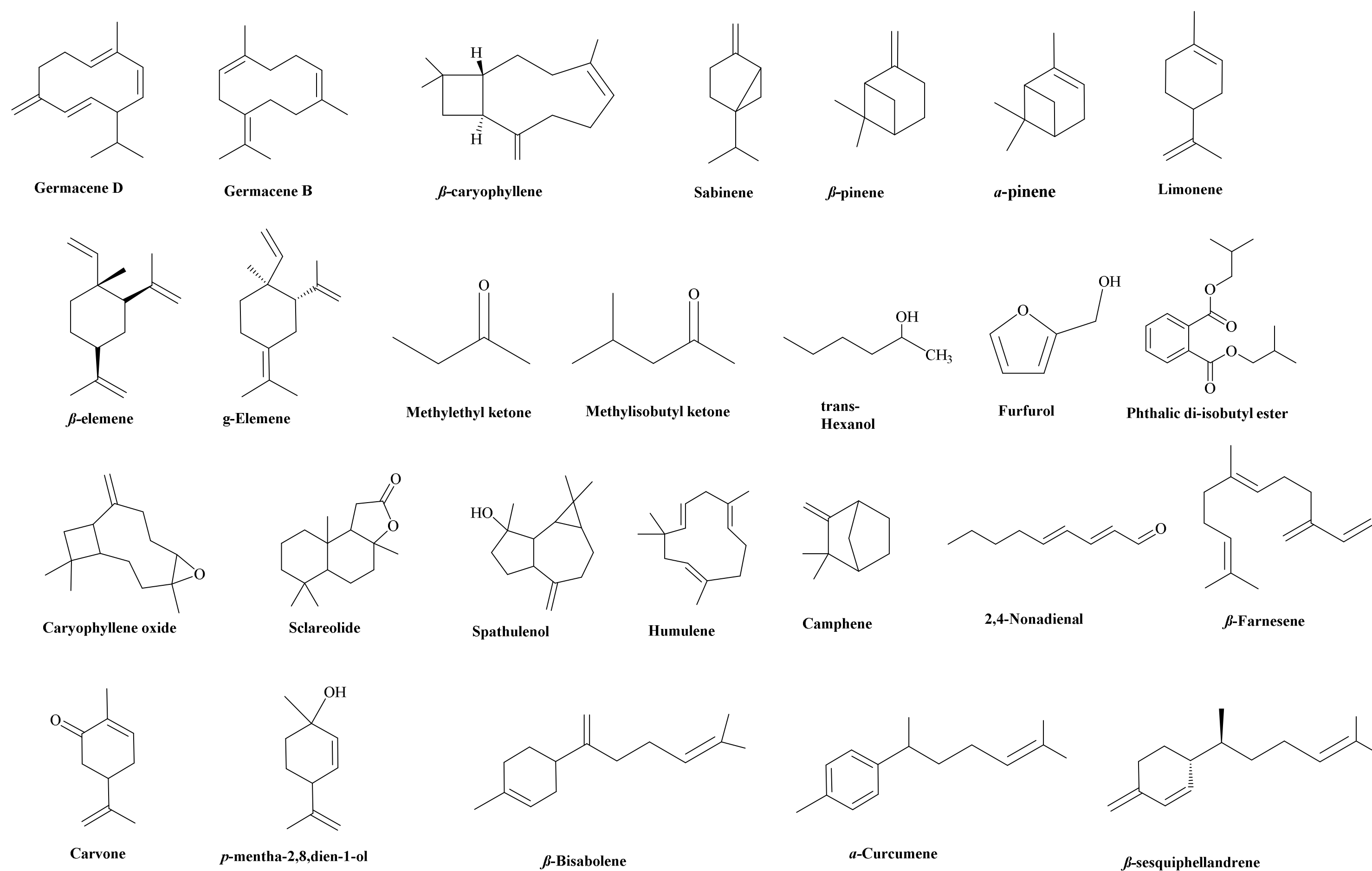


Fig. (6): Chemical structures of reported volatile constituents from Genus *Hedera*

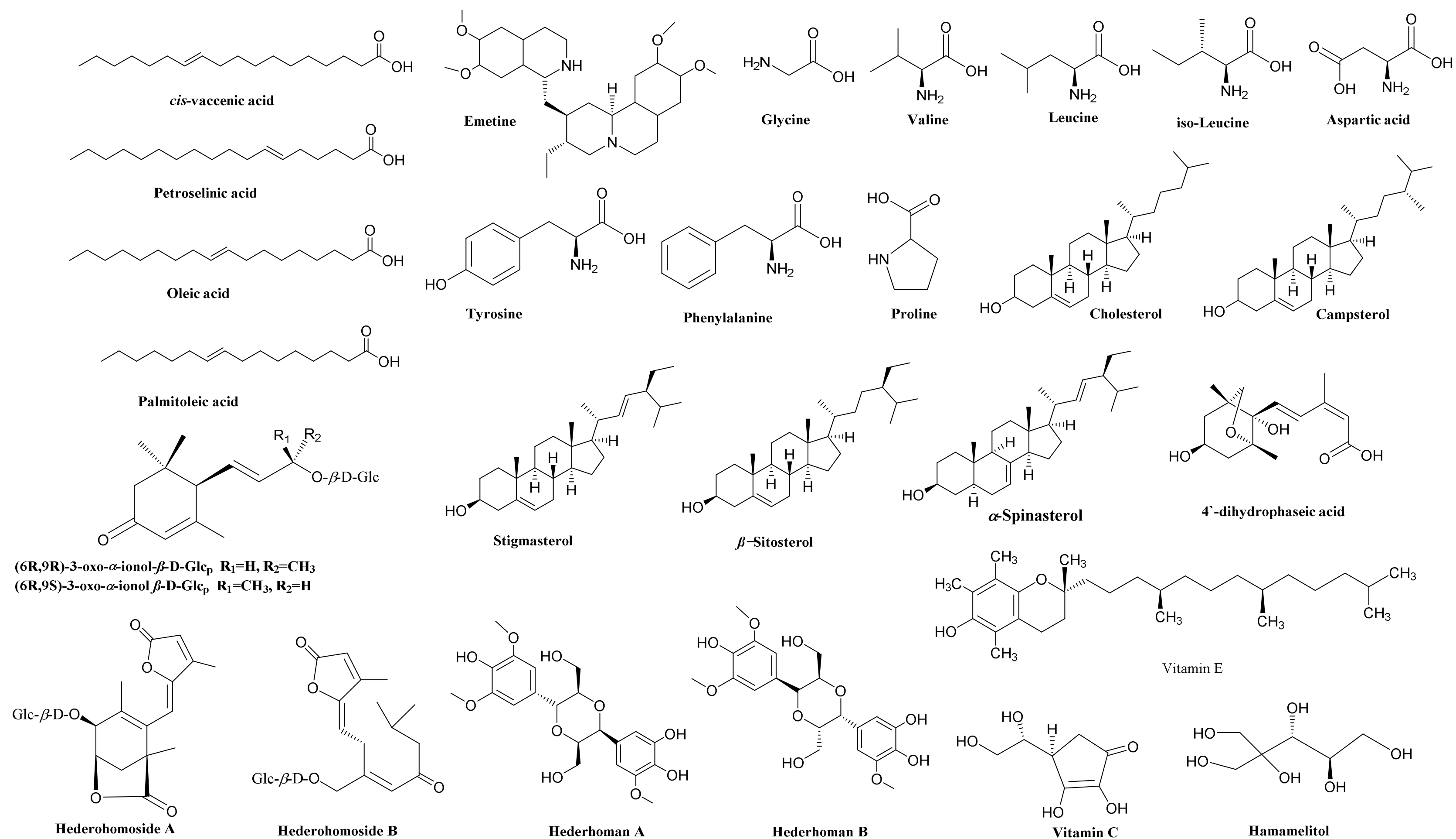


Fig. (7): Chemical structures of reported miscellaneous constituents from Genus *Hedera*