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Revisão

# *Helicteres* L. SPECIES (Malvaceae *SENSU LATO*) AS SOURCE OF NEW DRUGS: A REVIEW

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*Helicteres* genus, Malvaceae, has pantropical distribution, encompasses about 60 species, 31 of them found in Brazil. Species belonging to this genus are used for treatment of various diseases and aroused scientific interest in search for bioactive compounds present in these plants. In this context, this review aims to provide a complete and concise overview of scientific advances in phytochemical and pharmacological studies of these species and their use by folk medicine. The presented data were collected from scientific databases, '*Web of Science*', '*Scifinder*', '*Pubmed*', '*Sciencedirect*', and '*Google Scholar*', using the keyword '*Helicteres*'. The species *H. isora* and *H. angustifolia,* found in Asia, are the most explored scientifically, whereas studies of species of this genus found in Americas are still rare, being possible to highlight studies carried out in Brazil with *H. velutina* and *H. eichleri*. About 149 compounds were isolated and characterized in the genus, being emphasized terpenoids, flavonoids and lignoids. These species have demonstrated various pharmacological properties *in vitro* and *in vivo*, incluinding insecticide, antidiabetic, antitumor and hepatoprotective activities. The presented data show the importance of studies carried out isolating bioactive compounds from this genus that may be used in several diseases' treatment or/as prototypes to development of new drugs.

Keywords: *Helicteres* L.; secondary metabolite; ethnopharmacological relevance; scientific studies.

## INTRODUCTION

The use of natural products by mankind with the purpose of supplying physical and biological needs is an ancient practice, being the knowledge acquired transmitted throughout the generations.[1-3] Previous studies have allowed the association of chemical constituents present in the medicinal species and their respective pharmacological activities, based on experimental researches including knowledges of botany, chemistry, biochemistry and pharmacology, greatly contributing to the discovery of bioactive natural products.[4,5]

In this context, species of Sterculiaceae clade, Malvaceae *sensu lato*, have aroused great interest in the scientific environment and stand out for their importance in industrial, economic, medicinal, food and ornamental production, as well their chemical and biological properties.[6,7]

Among the genus belonging to this group, we highlight *Helicteres* L., whose biological and pharmacological effects of some species used in folk medicine were scientifically confirmed through the isolation, structural characterization and pharmacological activities developed by its secondary metabolites.[8]

*Helicteres* L. genus has pantropical distribuition, comprising approximately 60 species in America and Asia, with no species common to both continents. In Asia, the most studied species chemically and pharmacologically are *H. isora*, *H. angustifolia* and *H. hirsute*. China has about ten species, of which only one is endemic.[9]

In America, there are 38 species distributed from Mexico to Argentina, with no reports of occurence for Ecuador and Chile. Among the most scientifically studied species in the continent, we can highlight *H. sacarolha*, *H. eichleri* and *H. velutina*, the last two endemic in Brazil, which is considered the center of diversity of this genus in Americas, having a registered occurrence of 31 species, 23 of which are exclusive from cerrado, caatinga and dry forests.[10-12]

Based on the presented data, the objective of this review is to make a survey about the traditional use of *Helicteres* genus species, as well as evaluating their chemical and pharmacological potential to show the importance of this genus and provide a basis for future research.

## METHODOLOGY

Available information on traditional uses, phytochemical study, botanical characteristics and biological activities of *Helicteres* genus were collected from scientific databases: '*Web of Science*', '*Scifinder*', '*Pubmed*', '*Sciencedirect*', and '*Google Scholar*', using articles, books, dissertations and theses published until July 2019, using the keyword '*Helicteres*'. This way, we came across 173 scientific papers. The interest in scientific studies focusing on species of this genus for the development of new drugs has increased over the years due to the promising results of the scientific studies conducted with *Helicteres*.

The study selection and data extraction were performed by one author (DAF) and confirmed by others (EBA, MSRS, MFVS). The extracted data were summarized in tabular form and a narrative description was used to provide a summary of updated information.

## RESULTS AND DISCUSSION

### Botanical profile and pollination

The *Helicteres* L. species are characterized morphologically as erect shrubs or sub-bushes, with showy, zygomorph, pedicellate flowers usually pendulous and odorless (Figure 1), with a long androgynophore and ten transverse stamens grafted in to a yellow to red corolla; fruits are distinct, spiral capsules.[13-15]

Its showy flowers are strongly attracted to bats and hummingbirds, as described in studies with *H. ovata*,[16] *H. brevispira*, *H. sacarolha*,[17-19] and *H. lhotzkyana*.[14,20] *H. isora* flowers, present at Asia, are large and

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***Figure 1.*** *Helicteres plants. A) H. isora, B) H. angustifolia, C) H. sacarolha, D) H. brevispera, E) H. grazumifolia*[15]

open daily, being visited by birds and insects that assist in pollination during the day.[21]

## Ethnopharmacological relevance

Almost all parts of *Helicteres* L. plants, including roots, bark and aerial parts, are reported to be traditionally used in several countries and tribes for therapeutic purposes (Table 1).

The juice of *H. isora* root is used in Tradicional Chinese Medicine for diabetes treatment, while fruit extract is used in various intestinal disorders to relieve colic and as an anthelmintic medicine against tapeworm.[22-24]

The root tea of *H. angustifolia* is used to treat influenza symptoms and to inhibit tumor growth.[25] *H. sacarolha* preparations with roots and leaves, in form of decoction, infusion or maceration, are used for liver complications, ovarian inflammation, amenorrhea and blood purification,[8] while the aerial parts of *H. velutina* are used by indigenous tribe Pankarare/Brazil as insect repellent.[26]

Ethnopharmacological research with species of this genus acts as a subsidy to the pharmaceutical interest and registration of the empirical uses of medicinal plants in traditional communities associated with chemical-pharmacological tests generates useful knowledges to lead to the development of new drugs.

## Phytochemistry profile

In literature, 46 references on the phytochemistry field with species of *Helicteres* genus were found, 39 of which referring to the studies with *H. isora* and *H. angustifolia*. Furthemore, papers reporting research in this area with the species *H. hirsute*,[38,46] *H. vegae*,[47] *H. velutina*[12] and *H. eichleri*[48] were found, 149 compounds were isolated and identified from *Helicteres* (Table 2) among the most reported classes. All substances are compiled in the Table 2 (compounds) and Figure 2 (structures).

### *Terpenoids and steroids*

Terpenoids and its oxygenated, acetylated and dehydrogenated derivatives are hydrocarbons of plant origin.[84] Many of these molecules have biological activities that are used for the treatment of human diseases. These molecules have led to six major classes of drugs in the last century: steroids, tocopherols, texanes, artemisinins, ingenans and cannabinoids.[85,86]

Fifty terpenoids were isolated and identified from *H. isora*, *H. angustifolia*, *H. hirsuta*, *H. eichleri* and *H. velutina*, evidencing this class as the predominant compounds in *Helicteres* genus (Table 2). In a preliminary bioassay, cucurbitacins D (**4**) and J (**8**) exhibited significant inhibitory activities against hepatocellular carcinoma and malignant melanoma cells *in vitro*.[51]

Compounds 3β-*O* (*trans*-coumaroyl) betulinic acid (**15**), pyracrenic acid (**16**), 3β-acetoxy-27-[(4-hydroxybenzoyl)oxy]lup-20(29)-en-28-oic acid (**32**) and 3β-acetoxy-27-[(4-hydroxybenzoyl) oxy]olean-12-en-28-oic acid methyl (**39**), showed significant cytotoxic activities against human colorectal cancer and human gastric cancer cell lines *in vitro*.[44] The compound 10-methyl, 4-isopropenyl, dodecahydro-ethanophenanthrene (**48**) exhibited considerable antimicrobial and antispasmodic activities.[64]

Steroids are one of the less widespread classes in isolated from species of *Helicteres* genus, with only seven representatives (**50**-**56**).

Phytosteroids are steroidal substances extracted from plant species, the most common being β-sitosterol (**51**) and Stigmasterol (**52**). This class of substances has carbonic skeleton formed by the cyclopentanoperhydrophenanthrenic ring,[87] highlightin the β-sitosterol, which presented antimicrobial and larvicidal activities.[88,89]

### *Flavonoids and phenolic compounds*

Flavonoids represent one of the most important and diverse groups of phenolic compounds among natural products.[90,91] Among the phytotherapics currently studied, flavonoids have been highlighted due to their wide range of biological and/or pharmacological actions demonstrated under both experimental and human conditions.[92]

Twenty-nine flavonoids were isolated from *Helicteres* genus, with emphasis on heterosides (**69**),[36,71] sulphated (**78**-**80**) and heterosides glycosulphated (**65**-**67**).[12,36] Among those compounds, tiliroside (**70**) and 7,4′-di-*O*-methyl-8-*O*-sulphate flavone (**78**) have larvicidal activity against *Aedes aegypti*,[88] while 7,4'-*O*-methylisoscutellarein (**60**) have shown anti-inflammatory activity by inhibiting neutrophil recruitment and decreasing IL-1β and TNF-α production *in vitro*.[93]

Besides the flavonoids, it was possible to identify 18 phenolic compounds (**85**-**102**) with different nuclei, among them rosmarinic acid (**85**) isolated from *H. isora* fruits, *H. angustifolia* and *H. vegae* roots and *H. eichleri* aerial parts. Scientific studies of this substance have proven its antioxidant, anti-inflammatory, antifibrosis, hepatoprotective and antineoplasic activities.[94]

Some studies also report the compounds quantification in species of *Helicteres* genus, among which are total phenolic content, flavonoids and condensed tannins of *H. vegae*.[47] It was also accomplished the phenolics, flavonoids and saponins quantification of *H. hirsuta*[45,95,96] and *H. isora*, to evaluate their antioxidant potential.[97-99]

### *Lignoids*

Twenty-one lignoids were isolated and identified from *H. isora*, *H. angustifolia*, *H. hirsuta* and *H. velutina* species, most of them found in the roots and fruits. Yin *et al.* (2016)[57] isolated two benzofuran lignans of *H. angustifolia* that were evaluated for anti-complementary activity *in vitro* and showed potent activity when compared to heparin

**Table 1.** Species of *Helicteres* genus and their uses in folk medicine

| Scientific name/ Popular name | Medicinal parts | Traditional use | Therapeutic indications | References |
|---|---|---|---|---|
| *H. isora* / "Ulet-Ulet" | RT and BK | Decoction<br>Juice<br>Paste<br>Extract | Anthelmintic<br>Snake bites<br>Chronic nephritis<br>Gastric ulcers<br>Antidiabetic<br>Expectorant<br>Astringent<br>Anticolagogue<br>Antiasthmatic<br>Intestinal infections | 22-24,27-34 |
| | FR | Pod extracts | Anthelmintic<br>Intestinal infections<br>Vermifuges<br>Antiflatulence<br>Antispasmodic<br>Astringent<br>Antidiarrheal<br>Antidysenteric<br>Antipyretic | 22,24,27,29-32, 34-38 |
| | LV | Paste | Tanning | 30,39 |
| *H. angustifolia* / "Shan-Zhi-Ma" | RT and ST | Tea<br>Medicinal liquor | Analgesic<br>Anti-inflammatory<br>Antibacterial<br>Antiviral<br>Antitumoral | 25,40-42 |
| *H. sacarolha* / "Sacarolha" | RT and LV | Decoction<br>Infusion<br>Maceration | Antihypertensive<br>Antiulcerogenic<br>Antisyphilitic<br>Hepatoprotective<br>Anti-inflammatory<br>Amenorrhea<br>Blood clearance | 8,25,43 |
| *H. ovata* | * | * | Antisyphilitic<br>Blood clearance | 21,25 |
| *H. hirsuta* | RT | Decoction | Treatment of uterus pain<br>Antimalarial<br>Antidiabetic | 44,45 |
| *H. velutina* / "Pitó" | AP | * | Insect repellent | 26 |

*not reported in the literature. RT: Roots; BK: Barks; FR: Fruits; LV: Leaves; ST: Stems; AP: Aerial Parts.

(positive control). Tezuka *et al*. (2000)[74] isolated and identified six dimeric neolignans from fruits of *H. isora*: Helicterins B (**120**), C (**115**), D (**117**), E (**116**) and F (**118**), which showed mild inhibitory activity against avian myeloblastosis virus reverse transcriptase (AMV-RT), having an emphasis on the inhibitory activity of Helicterins A (**119**), which was identical to the antineoplasic drug doxirubicin, with an $IC_{50}$ of 66 μM. This can be of interest for the development of new therapeutic alternatives.

*Quinones*

Quinones are structurally characterized as cyclic α, β-dienics, and have considerable toxicological and pharmacological interests due to their biooxidation-reduction properties and ability to catalyze biological electrical transfer.[100] However, biological studies involving isolated quinones of *Helicteres* species are scarce, as it is necessary to investigate possible biological actions not yet explored. So far, ten quinones have been isolated and identified in the studied genus (**123**-**132**), and the compounds that best represent this class were sesquiterpene quinones and *O*-benzoquinones, isolated from *H. angustifolia* roots.[40,42,51]

*Other compounds*

Beyond to previously detailed compounds, other classes of metabolites, such as amines, saponins, lactones, coumarins, alcohols, fatty acids, alkaloids, pheophytins and tannins (**133**-**149**) (Table 2, Figure 1), were less frequently detected in this genus.

Aleykutty & Akhila (2012),[80] by means of a computational approach, predicted the antidiabetic potential of the chemical constituents identified in *H. isora*, especially the indolalkylamine, Yohimbine (**142**), which presented the best binding energy with the enzyme aldose reductase and the insulin receptor protein, pharmacological targets for glycemic control.

## Pharmacology study

Pharmacological potential of *Helicteres* species has gained prominence, especially with *H. isora* and *H. angustifolia*, that have a long history of use in traditional Chinese medicine. Researches have been developed about antidiabetic, antiulcerogenic and antitumor activities within *Helicteres* species in order to confirm the activities reported by folk medicine (Table 3).

**Table 2.** Isolated compounds from *Helicteres* genus

| Nº | Name | Source | Literature |
|---|---|---|---|
| | **Terpenoids** | | |
| **1** | Cucurbitacin B | RT of ***H.i.*** | 24,49 |
| **2** | Cucurbitacin B 2-sulfate | RT of ***H.a.*** | 50 |
| **3** | Isocucurbitacin B | RT of ***H.i.*** | 24,49 |
| **4** | Cucurbitacin D | | |
| **5** | Cucurbitacin E | | |
| **6** | Cucurbitacin G 2-*O*-β-D-glucopyranoside | | |
| **7** | Cucurbitacin I | RT of ***H.a.*** | 50-53 |
| **8** | Cucurbitacin J | | |
| **9** | Isocurcubitacin D | | |
| **10** | Hexanorcucurbitacin I | | |
| **11** | Lup-20(29)-em-3β-ol | RT of ***H.h.***<br>AP of ***H.e.*** | 48,54 |
| **12** | Betulinic acid | RT of ***H.i.***, ***H.a.*** and ***H.h.*** | 51,54,55 |
| **13** | 3β-benzoylbetulinic acid | RT of ***H.h.*** | 54 |
| **14** | Betulinic acid methyl ester | | |
| **15** | 3β-*O* (*trans*-coumaroyl) betulinic acid | RT of ***H.a.*** | 44 |
| **16** | Pyracrenic acid | RT of ***H.a.*** and ***H.h.*** | 53 |
| **17** | 3β-*O*-(*trans*-feruloyl) betulinic acid | | |
| **18** | 3β-*O*-(*trans*-coumaroyl) botulin | | |
| **19** | 3β-*O*-(*cis*-coumaroyl) botulin | RT of ***H.a.*** | 44 |
| **20** | 3β-*O*-(*trans*-caffeoyl) betulin | | |
| **21** | 3β-*O*-(*trans*-feruloyl) betulin | | |
| **22** | 3β-acetoxybetulinic acid | RT of ***H.a.***<br>AP of ***H.h.*** | 52,56 |
| **23** | 3-acetoxybetulin | | |
| **24** | 3β-27-diacetoxy-lup-20(29)en-28-oic methyl ester | | |
| **25** | 3β-acetoxy-27-benzoyloxylup-20(29)-en-28-oic acid | | |
| **26** | 3β-acetoxylup-20(29)-en-28-ol | | |
| **27** | 3β-hydroxylup-20(29)-en-28-oic acid 3-caffeate | | |
| **28** | 3β-hydroxy-27-benzoyloxylup-20(29)-en-28-oic acid | RT of ***H.a.*** | 35,44,51,53,55 |
| **29** | 3β-hydroxy-27-benzoyloxylup-20(29)-en-28-oic acid methyl ester | | |
| **30** | Methyl helicterate | | |
| **31** | 3β-acetoxy-27-[(*E*)-cinnamoyloxy]lup-20(29)-en-28-oic acid methyl ester | | |
| **32** | 3β-acetoxy-27-[(4-hydroxybenzoyl)oxy]lup-20(29)-en-28-oic acid | | |
| **33** | Cylicodiscic acid | | |
| **34** | Simiarenol | AP of ***H.h.*** | 56 |
| **35** | Isorin | RT and FR of ***H.i.*** | 55,57 |
| **36** | 3β-hydroxyolean-12-en-27-benzoyloxy-28-oate | | |
| **37** | 3β-*O*-(*p*-hydroxy-(*E*)-cinnamoyl)-12 oleanen-28-oic acid | | |
| **38** | Helicterilic acid | RT of ***H.a.*** | 44,58-60 |
| **39** | 3β-acetoxy-27-[(4-hydroxybenzoyl)oxy]olean-12-en-28-oic acid methyl ester | | |
| **40** | 3β-acetoxy-27-(benzoyloxy)olean-12-en-28-oic acid methyl ester | | |
| **41** | Ursolic acid | RT of ***H.a.***<br>AP of ***H.e.*** | 48,61 |
| **42** | 3α-hydroxy-urs-12-en-28-oic acid | | |
| **43** | 3α-hydroxy-olean-12-en-28-oic acid | AP of ***H.e.*** | 48 |
| **44** | Micromeric acid | | |
| **45** | Oleanolic acid | RT of ***H.i.***, ***H.a.***<br>AP of ***H.vel.*** | 12,62,63 |
| **46** | 3β-acethoxy-olean-12-en-28-oic acid | AP of ***H.vel.*** | 12 |
| **47** | 3β-sterearyloxy-olean-12-ene | | |
| **48** | 10-methyl, 4-isopropenyl, dodecahydro-ethanophenanthrene | RT of ***H.i.*** | 64 |
| **49** | Methyl helicterilate | RT of ***H.a.*** | 65 |

**Table 2.** Isolated compounds from *Helicteres* genus (cont.)

| Nº | Name | Source | Literature |
|---|---|---|---|
| | **Steroids** | | |
| **50** | β-sitosterol glucoside | RT of ***H.i.***, ***H.a.*** AP of ***H.vel.*** | 12,24,66 |
| **51** | β-sitosterol | RT of ***H.i.***, ***H.a.*** AP of ***H.e.*** | 24,48,67,68 |
| **52** | Stigmasterol | RT of ***H.h.*** AP of ***H.e***. | 48,54 |
| **53** | Heligenin A | RT of ***H.a.*** | 51,52,66 |
| **54** | Heligenin B | | |
| **55** | 2α,7β,20α-Trihydroxy-3β,21-dimethoxy-5-pregnen | | |
| **56** | 3β-ergost-5-en-3-ol | | |
| | **Flavonoids** | | |
| **57** | Kaempferol-3-*O*-galactoside | | 69 |
| **58** | Herbacetin-8-*O*-glucuronide | | |
| **59** | 7-*O*-methylisoscutellarein | AP of ***H.h.*** | 54,56,70 |
| **60** | 7,4'-di-*O*-methylisoscutellarein | | |
| **61** | Isoscutellarein 4'-methyl ether 8-*O*-β-D-glucopyranoside | | |
| **62** | Isoscutellarein 4'-methyl ether 8-*O*-β-D-glucuronide 6''-*n*-butyl ester | FR of ***H.i.*** | 36 |
| **63** | Isoscutellarein 4'-methyl ether 8-*O*-β-D-glucuronide | | |
| **64** | Isoscutellarein 4'-methyl ether 8-*O*-β-D-glucuronide 2''-sulfate | | |
| **65** | Isoscutellarein 4'-methyl ether 8-*O*-β-D-glucuronide 2'',4''-disulfate | | |
| **66** | Isoscutellarein 8-*O*-β-D-glucuronide 2'',4''-disulfate | | |
| **67** | Kaempferol-3-*O*-β-D-glucopyranoside | FR of ***H.i.*** RT of ***H.a.*** | 51,55,57 |
| **68** | Kaempferol | FR of ***H.i.*** AP of ***H.vel.*** | 12,57 |
| **69** | Tiliroside | FR of ***H.i.*** RT of ***H.a.*** AP of ***H.vel.*** | 12,52,55,57 |
| **70** | 5,7,8-trihydroxy-4′-methoxyflavone | FR of ***H.i.*** AP of ***H.a.*** | 55,57 |
| **71** | 3',5,7,8-tetrahydroxy-4'-methoxyflavone | FR of ***H.i.*** | 71 |
| **72** | Takakin 8-*O*-β-D-glucuronide 6-methyl ester | RT of ***H.a***. | 72 |
| **73** | Takakin 8-*O*-β-D-glucuronide 2-sodium sulfate | | |
| **74** | Takakin 8-*O*-β-D-glucuronide | | |
| **75** | 8-O-β-D-glucuronyl-hypolaetin 4'-methyl ether | | |
| **76** | 5,8-dihydroxy-7,4'-dimethoxyflavone | LV of ***H.i.*** RT of ***H.a.*** AP of ***H.vel.*** and ***H.h.*** | 12,51,54,69 |
| **77** | Tricin | RT of ***H.a.*** | 66 |
| **78** | 7,4'-di-*O*-metil-8-*O*-sulphate flavone | AP of ***H.vel.*** | 12 |
| **79** | 5,4'-di-hydroxy-7-methoxy-8-*O*-sulphate flavone | | |
| **80** | 5,6-di-hydroxy-7,4'-methoxy-8-*O*-sulphate flavone | | |
| **81** | Hesperidin | FR of ***H.i.*** | 36,55,57 |
| **82** | Viscumside A | | |
| **83** | 3',5,7,8-tetrahydroxy-4'-methoxyflavone 8-*O*-β-d-glucopyranosiduronic acid methyl ester | | |
| **84** | 4',5,7,8-tetrahydroxyflavone 8-*O*-β-D-glucopyranosiduronic acid methyl ester | | |
| | **Compounds Phenolics** | | |
| **85** | Rosmarinic acid | FR of ***H.i.*** RT of ***H.a.***, ***H.veg.*** AP of ***H.e.*** | 36,55 |
| **86** | 4'-*O*-β-D-glucopyranosyl rosmarinic acid | FR of ***H.i.*** | 38 |
| **87** | 4,4'-*O*-di-β-D-glucopyranosyl rosmarinic acid | | |
| **88** | 4'-*O*-β-D-glucopyranosyl isorinic acid | | |
| **89** | 3'-*O*-(8″-*Z*-caffeoyl) rosmarinic acid | LV of ***H.veg.*** | 47 |
| **90** | 3-(3,4-dimethoxyphenyl)-2-propenal | RT of ***H.a.*** | 51,52 |
| **91** | Catechol | RT of ***H.i.*** | 24 |
| **92** | 4-hydroxybenzoic acid | RT of ***H.h.*** | 54 |

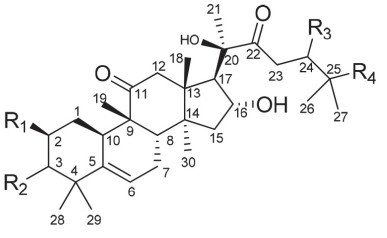
**Table 2.** Isolated compounds from *Helicteres* genus (cont.)

| Nº | Name | Source | Literature |
|---|---|---|---|
| | **Compounds Phenolics** | | |
| **93** | 3,4-dihydroxybenzoic acid methyl ester | RT of ***H.h.*** | 54 |
| **94** | 4-hydroxy-3,5-dimethoxybenzoic acid | | |
| **95** | Syringic acid-4-*O*-α-L-rhamnopyanoside | RT of ***H.a.*** | 52 |
| **96** | Protocatechuic aldehyde | | |
| **97** | Gallic acid | RT of ***H.i.*** | 24 |
| **98** | Vanillin | LV of ***H.i.*** | 24 |
| **99** | Coniferyl alcohol | RT of ***H.a.*** | 52 |
| **100** | Caffeic acid | RT of ***H.i.*** | 24 |
| **101** | *p*-Coumaric acid | LV of ***H.i.*** | 24 |
| **102** | Methyl caffeate | AP of ***H.h.*** | 54 |
| | **Lignoids** | | |
| **103** | Lariciresinol | | |
| **104** | Hedyotol C 7″-*O*-β-D-glucopyranoside | RT of ***H.a.*** | 51,57 |
| **105** | Hedyotol D 7″-*O*-β-D-glucopyranoside | | |
| **106** | (+)-pinoresinol | RT of ***H.a.***, ***H.h.*** AP of ***H.vel.*** | 12,46 |
| **107** | (+/-)-medioresinol | | |
| **108** | (+/-)-syringaresinol | RT of ***H.a.*** and ***H.h.*** | 46,51 |
| **109** | (-)-boehmenan | | |
| **110** | (-)-boehmenan H | | |
| **111** | (+/-)-*trans*-dihydrodiconiferyl alcohol | RT of ***H.a.*** FR of ***H.i.*** | 46,51,73 |
| **112** | (7*S*,8*R*)-Urolignoside | RT of ***H.a.*** | 52 |
| **113** | (7*S*,8*R*)-Dihydrodehydrodiconiferyl alcohol | RT of ***H.a.*** and ***H.h.*** | 12,57 |
| **114** | Helisorin | | |
| **115** | Helicterins C | | |
| **116** | Helicterins E | | |
| **117** | Helicterins D | | |
| **118** | Helicterins F | FR of ***H.i.*** | 73,74 |
| **119** | Helicterins A | | |
| **120** | Helicterins B | | |
| **121** | Helisterculins A | | |
| **122** | Helisterculins B | | |
| | **Quinones** | | |
| **123** | Perezone | | |
| **124** | 2,6-Dimethoxy-*p*-benzoquinone | | |
| **125** | 8-acetyl-9-hydroxy-3-methoxy-7-methyl-1-phenalenon | | |
| **126** | Heliquinone | | |
| **127** | Heliquinone methyl ether | | |
| **128** | Mansonone F | RT of ***H.a.*** | 40,42,57,66,75 |
| **129** | Mansonone E | | |
| **130** | Mansonone H | | |
| **131** | Mansonone M | | |
| **132** | 6-[2-(5-acetyl-2,7-dimethyl-8-oxo-bicyclo[4.2.0]octa-1,3,5-trien-7-yl)-2-oxo-ethyl]-3,9-dimethylnaphtho[1,8-bc]pyran-7,8-dione | | |
| | **Other compounds** | | |
| **133** | Malatyamine ethyl ester (Amine) | RT of ***H.i.*** | 53,76-79 |
| **134** | Diosgenin (Saponin) | | |
| **135** | 6,7-dihydroxy-3,8,11-trimethylcyclohexo-[d,e]-coumarin | RT of ***H.a.*** | 51,64 |
| **136** | 6,7,9α-trihydroxy-3,8,11α-trimethylcyclohexo-[d,e]-coumarin (Coumarin) | | |
| **137** | Tetratriacontanol (Alcohol) | LV of ***H.i.*** | 67 |
| **138** | Tetratriacontanoic acid (Fatty acid) | | |
| **139** | Palmitic acid (Fatty acid) | LV of ***H.i.*** AP of ***H.vel*** | 12,24 |
| **140** | Aliphatic alcohol decanol (Alcohol) | AP of ***H.vel.*** and ***H.e.*** | 12,48 |
| **141** | Helicterone A (Alkaloid) | RT of ***H.a.*** | 52 |
| **142** | Yohimbine (Alkaloid) | FR of ***H.i.*** | 80 |
| **143** | Pheophytin A | RT of ***H.i.*** AP of ***H.vel.*** | 12,81 |
| **144** | Pheophytin B | | |

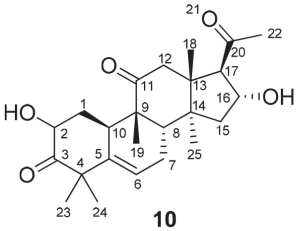
**Table 2.** Isolated compounds from *Helicteres* genus (cont.)

| Nº | Name | Source | Literature |
|---|---|---|---|
| **145** | $13^2$-hydroxy-($13^2$-*R*)-pheophytin a | AP of ***H.vel.*** | 12 |
| **146** | $13^2$-hydroxy-($13^2$-*S*)-pheophytin a | | |
| **147** | Ellagic acid (Tannin) | RT of ***H.i.*** | 82,83 |
| **148** | 3,6,9-trimethyl-pyrano[2,3,4-de]chromen-2-one (Lactone) | RT of ***H.a.*** | 75 |
| **149** | 4-4'-sulfinylbis(2-(*tert*-butyl)-5-methylphenol | AP of ***H.h.*** | 56,70 |

***H.i.*****:** *H. isora*; ***H.a.*****:** *H. angustifolia*; ***H.vel.*****:** *H. velutina*; ***H.h.*****:** *H. hirsuta*; ***H.veg.*****:** *H. vegae*; ***H.e.*****:** *H. eichleri*. RT: Roots; AP: Aerial Parts; FR: Fruits; LV: Leaves.



**1.** $R_1$: H; $R_2$: =O; $R_3$: H; $R_4$: $OCOCH_3$; $\Delta^{23,24}$
**2.** $R_1$: $HSO_3$; $R_2$: H; $R_3$: H; $R_4$: $OCOCH_3$; $\Delta^{23,24}$
**3.** $R_1$: =O; $R_2$: OH; $R_3$: H; $R_4$: $OCOCH_3$; $\Delta^{23,24}$
**4.** $R_1$: OH; $R_2$: =O; $R_3$: H; $R_4$: OH; $\Delta^{23,24}$
**5.** $R_1$: OH; $R_2$: =O; $R_3$: H; $R_4$: $OCOCH_3$; $\Delta^{23,24}$; $\Delta^{1,2}$
**6.** $R_1$: OGlc; $R_2$: =O; $R_3$: OH; $R_4$: OH
**7.** $R_1$: OH; $R_2$: =O; $R_3$: H; $R_4$: OH; $\Delta^{23,24}$; $\Delta^{1,2}$
**8.** $R_1$: OH; $R_2$: =O; $R_3$: OH; $R_4$: OH; $\Delta^{1,2}$
**9.** $R_1$: =O; $R_2$: OH; $R_3$: H; $R_4$: OH; $\Delta^{23,24}$



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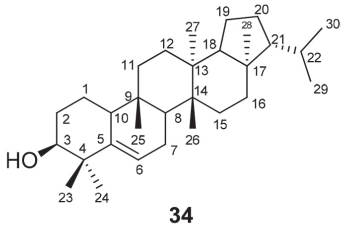
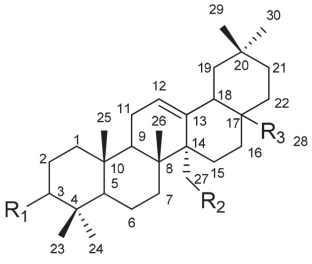
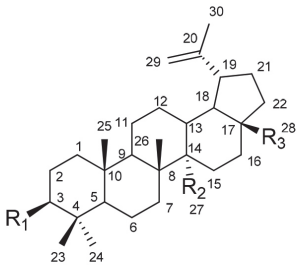


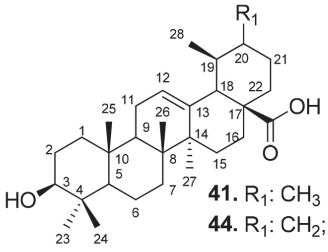
**34**



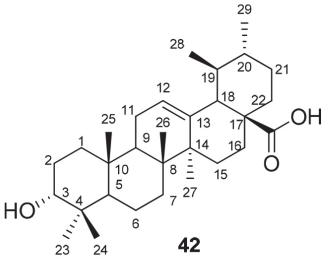
**35.** $R_1$: OH; $R_2$: OAc; $R_3$: H
**36.** $R_1$: OH; $R_2$: benzoyl; $R_3$: $COOCH_3$
**37.** $R_1$: *O*-cinnamoyl; $R_2$: H; $R_3$: COOH
**38.** $R_1$: OAc; $R_2$: *O*-4-hydroxybenzoyl; $R_3$: OAc
**39.** $R_1$: OAc; $R_2$: *O*-4-hydroxybenzoyl; $R_3$: $COOCH_3$
**40.** $R_1$: OAc; $R_2$: *O*-PhCO; $R_3$: $COOCH_3$



**11**. $R_1$: OH; $R_2$: $CH_3$; $R_3$: H
**12**. $R_1$: OH; $R_2$: $CH_3$; $R_3$: COOH
**13**. $R_1$:*O*-benzoyl; $R_2$: $CH_3$; $R_3$: COOH
**14**. $R_1$: OH; $R_2$: $CH_3$; $R_3$: $COOCH_3$
**15**. $R_1$: *O-trans*-coumaroyl; $R_2$: $CH_3$; $R_3$: COOH
**16**. $R_1$: *O-trans*-caffeoyl; $R_2$: $CH_3$; $R_3$: COOH
**17**. $R_1$: *O-trans*-feruloyl; $R_2$: $CH_3$; $R_3$: COOH
**18**. $R_1$: *O-trans*-coumaroyl; $R_2$: $CH_3$; $R_3$: $CH_2OH$
**19**. $R_1$: *O-cis*-coumaroyl; $R_2$: $CH_3$; $R_3$: $CH_2OH$
**20**. $R_1$: *O-trans*-caffeoyl; $R_2$: $CH_3$; $R_3$: $CH_2OH$
**21**. $R_1$: *O-trans*-feruloyl; $R_2$: $CH_3$; $R_3$: $CH_2OH$
**22**. $R_1$:$OCOCH_3$; $R_2$: $CH_3$; $R_3$: COOH
**23**. $R_1$:$OCOCH_3$; $R_2$: $CH_3$; $R_3$: $CH_2OH$
**24.** $R_1$=$R_2$: OAc; $R_3$: COOH
**25.** $R_1$: OAc; $R_2$: benzoyloxy; $R_3$:COOH
**26.** $R_1$: OAc; $R_2$=H; $R_3$=OH
**27.** $R_1$: caffeate; $R_2$=H; $R_3$=COOH
**28.** $R_1$: OH; $R_2$:benzoyloxy; $R_3$=COOH
**29.** $R_1$: OH; $R_2$: benzoyloxy; $R_3$=$COOCH_3$
**30.** $R_1$: OCOOH; $R_2$: $CH_2$-benzoyloxy; $R_3$=$COOCH_3$
**31**. $R_1$: OAc; $R_2$=$CH_2$-*O-trans*-cinnamoyl; $R_3$=$COOCH_3$
**32**: $R_1$: OAc; $R_2$=$CH_2$-*O*-4-hydroxybenzoyl; $R_3$=COOH
**33**: $R_1$: OH; $R_2$=$CH_2OH$; $R_3$=COOH



**41.** $R_1$: $CH_3$
**44.** $R_1$: $CH_2$; $D^{20,30}$



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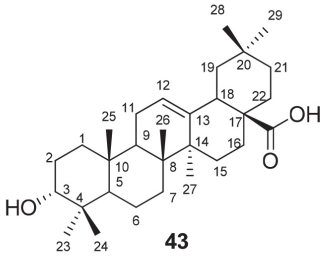

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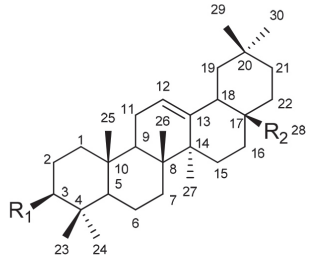
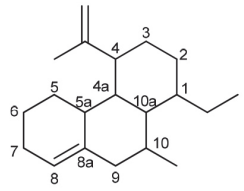


**45.** $R_1$: OH; $R_2$: COOH
**46.** $R_1$: $OCOCH_3$; $R_2$: COOH
**47.** $R_1$: Phytil; $R_2$: H

***Figure 2.*** *Compounds isolated from Helicteres species*



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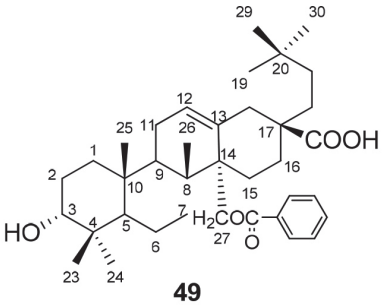

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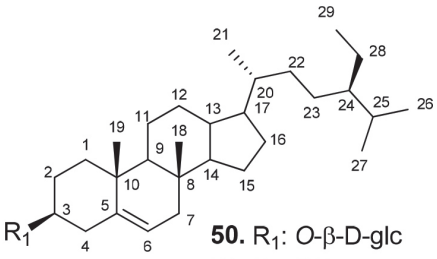
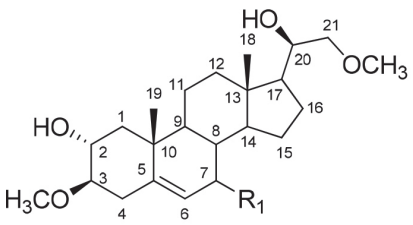
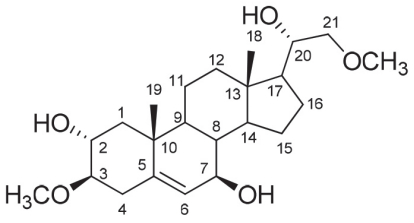


**50.** $R_1$: *O*-β-D-glc
**51.** $R_1$: OH
**52.** $R_1$: OH; $\Delta^{22,23}$



**53.** $R_1$: =O
**54.** $R_1$: OH



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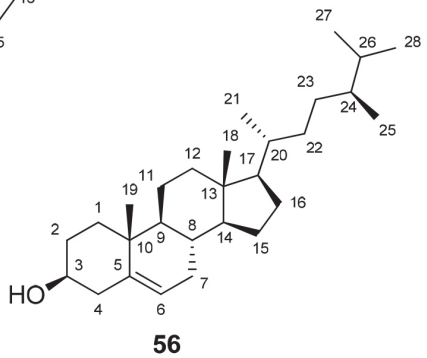

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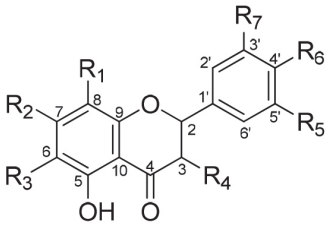
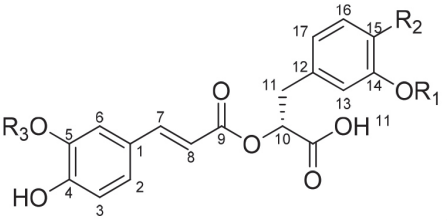
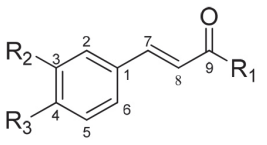


**57.** $R_1$=$R_3$=$R_5$=$R_7$: H; $R_2$=$R_6$: OH; $R_4$: *O*-β-D-galactoside; $\Delta^{2,3}$
**58.** $R_1$:*O*-β-D-galactoside; $R_3$=$R_5$=$R_7$: H; $R_2$=$R_6$=$R_4$: OH; $\Delta^{2,3}$
**59.** $R_1$=$R_6$: OH; $R_2$: $OCH_3$; $R_3$=$R_4$=$R_5$=$R_7$: H; $\Delta^{2,3}$
**60.** $R_1$: OH; $R_2$: $OCH_3$; $R_3$=$R_4$=$R_5$=$R_7$: H; $R_6$: $OCH_3$; $\Delta^{2,3}$
**61.** $R_1$: *O*-β-D-glucupyranoside; $R_2$: OH; $R_3$=$R_4$=$R_7$: H; $R_6$: $OCH_3$; $\Delta^{2,3}$
**62.** $R_1$: *O*-β-D-glcuronide, 6'' *n*-buthyl ester; $R_2$: OH; $R_3$=$R_4$=$R_5$=$R_7$: H; $R_6$: $OCH_3$; $\Delta^{2,3}$
**63.** $R_1$: *O*-β-D-glcuronide; $R_2$: OH; $R_3$=$R_4$=$R_5$=$R_7$: H; $R_6$: $OCH_3$; $\Delta^{2,3}$
**64.** $R_1$: *O*-β-D-glcuronide, 2'' sulphate; $R_2$: OH; $R_3$=$R_4$=$R_5$=$R_7$: H; $R_6$: $OCH_3$; $\Delta^{2,3}$
**65.** $R_1$: *O*-β-D-glcuronide, 2'', 4'' sulphate; $R_2$: OH; $R_3$=$R_4$=$R_5$=$R_7$: H; $R_6$: $OCH_3$; $\Delta^{2,3}$
**66.** $R_1$: *O*-β-D-glcuronide, 2'', 4'' sulphate; $R_2$=$R_6$: OH; $R_3$=$R_4$=$R_5$=$R_7$: H; $\Delta^{2,3}$
**67.** $R_1$=$R_3$=$R_5$=$R_7$: H; $R_2$=$R_6$: OH; $R_4$: *O*-β-D-glc; $\Delta^{2,3}$
**68.** $R_1$=$R_3$=$R_5$=$R_7$: H; $R_2$=$R_4$=$R_6$: OH; $\Delta^{2,3}$
**69.** $R_1$: H; $R_2$= $R_6$: OH; $R_3$: H; $R_4$: *O*-glc-6''-p-coumaroyl; $R_5$=$R_7$: $\Delta^{2,3}$
**70.** $R_1$=$R_2$: OH; $R_3$=$R_4$=$R_5$=$R_7$: H; $R_6$: $OCH_3$; $\Delta^{2,3}$
**71.** $R_1$=$R_2$=$R_7$: OH; $R_3$=$R_4$=$R_5$: H; $R_6$: $OCH_3$; $\Delta^{2,3}$
**72.** $R_1$: *O*-β-D-glucuronide, 6'' methyl ester; $R_2$: OH; $R_3$=$R_4$=$R_7$: H; $R_6$: $OCH_3$; $\Delta^{2,3}$
**73.** $R_1$: *O*-β-D-glucuronide, 2'' sodium sulphate; $R_2$: OH; $R_3$=$R_4$=$R_7$: H; $R_6$: $OCH_3$; $\Delta^{2,3}$
**74.** $R_1$: *O*-β-D-glucuronide; $R_2$: OH; $R_3$=$R_4$=$R_7$: H; $R_6$: $OCH_3$; $\Delta^{2,3}$
**75.** $R_1$: *O*-β-D-glucuronide; $R_3$=$R_4$=$R_5$=$R_7$: H; $R_2$=$R_7$: OH; $R_6$: $OCH_3$; $\Delta^{2,3}$
**76.** $R_1$: OH; $R_2$=$R_6$: $OCH_3$; $R_3$=$R_4$=$R_5$=$R_7$: H; $\Delta^{2,3}$
**77.** $R_1$=$R_3$=$R_4$: H; $R_2$=R6: OH; $R_5$=$R_7$: $OCH_3$; $\Delta^{2,3}$
**78.** $R_1$: $OSO_3H$; $R_2$=$R_6$: $OCH_3$; $R_3$=$R_4$= $R_5$=$R_7$: H; $\Delta^{2,3}$
**79.** $R_1$: $OSO_3H$; $R_2$: $OCH_3$; $R_3$=$R_4$= $R_5$=$R_7$: H; $R_6$: OH; $\Delta^{2,3}$
**80.** $R_1$: $OSO_3H$; $R_2$=$R_6$: $OCH_3$; $R_3$: OH; $R_4$=$R_5$=$R_7$: H; $\Delta^{2,3}$
**81**. $R_1$=$R_3$=$R_4$=$R_5$: H; $R_2$: *O*-rhamnosyl, 6'' glc; $R_6$: OH; $R_7$: $OCH_3$
**82**. $R_1$=$R_3$=$R_4$=$R_5$: H; $R_2$: *O*-β-D-glc; $R_6$: OH; $R_7$: $OCH_3$
**83.** $R_1$: *O*-β-D-glucopyranosiduronic acid methyl ester; $R_3$=$R_4$=$R_5$: H; $R_6$: OCH3; $R_7$: OH
**84.** $R_1$: *O*-β-D-glucopyranosiduronic acid methyl ester; $R_3$=$R_4$=$R_5$=$R_7$: H; $R_6$: OH;

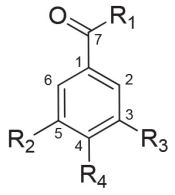
***Figure 2.*** *Compounds isolated from Helicteres species (cont.)*



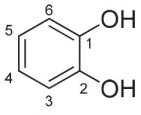
**85**. $R_1$=$R_3$: H; $R_2$=OH;
**86**. $R_1$: H; $R_2$: OH; $R_3$: β-D-gluc
**87**. $R_1$: β-D-glc; $R_2$: OH; $R_3$: β-D-glc
**88**. $R_1$=$R_2$: H; $R_3$: β-D-gluc
**89**. $R_1$: H; $R_2$: OH; $R_3$: caffeoyl



**90.** $R_1$: H; $R_2$=R3: $OCH_3$
**100**. $R_1$=$R_3$: OH; $R_2$=H
**101.** $R_1$=$R_2$=$R_3$: OH
**102.** $R_1$: $OCH_3$; $R_2$=$R_3$: OH



**92.** $R_1$=$R_4$: OH; $R_2$=$R_3$: H
**93.** $R_1$: $OCH_3$; $R_2$: H $R_3$=$R_4$: OH
**94.** $R_1$=$R_4$: OH; $R_2$=$R_3$: $OCH_3$
**95.** $R_1$: OH; $R_2$=$R_3$: $OCH_3$; $R_4$: α-L-*O*-Rhamnosyl
**96.** $R_1$=$R_2$: H; $R_3$=$R_4$: OH
**97.** $R_1$: H; $R_2$=$R_3$=$R_4$: OH
**98.** $R_1$=$R_2$: H; $R_3$: $OCH_3$; $R_4$: OH



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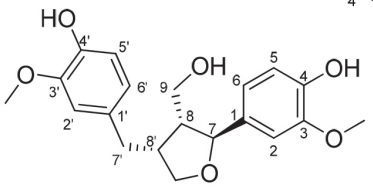
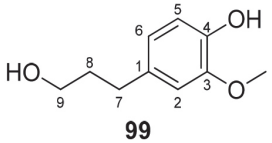


**103**



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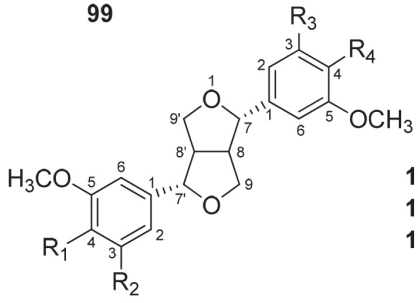
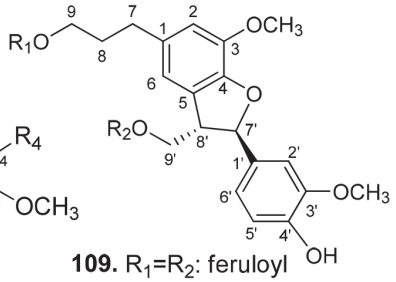
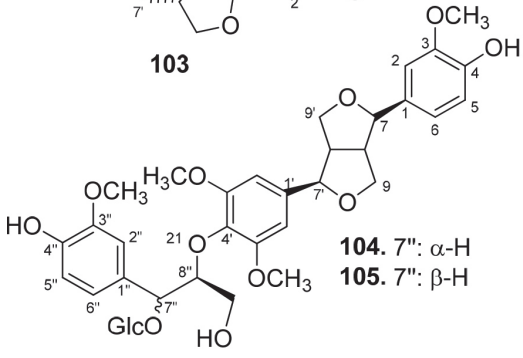


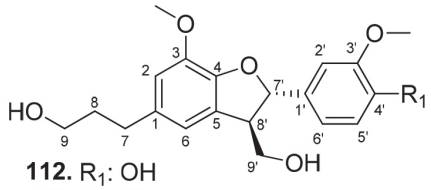
**106.** $R_1$=$R_4$: OH; $R_2$=$R_3$: OH
**107.** $R_1$=$R_4$: OH; $R_2$: $OCH_3$; $R_3$: H
**108.** $R_1$=$R_4$: OH; $R_2$=$R_3$: $OCH_3$



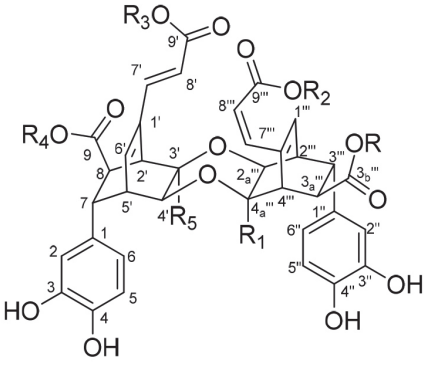
**109.** $R_1$=$R_2$: feruloyl
**110.** $R_1$: feruloyl; $R_2$: H
**111.** $R_1$=$R_2$: H



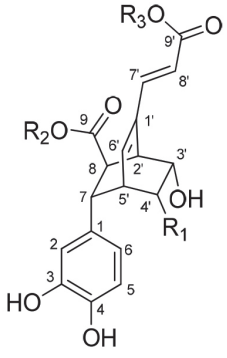
**104.** 7": α-H
**105.** 7": β-H



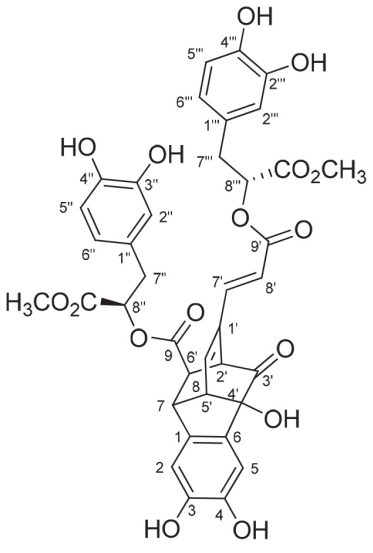
**112.** $R_1$: OH
**113.** $R_1$: Glc



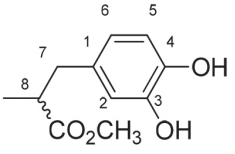
**115.** $R_1$=$R_5$: $OCH_3$; R: $CH_3$; ; $R_2$=$R_3$=$R_4$: **X**
**116.** $R_1$: $OCH_3$; R: $CH_3$; ; $R_2$=$R_3$=$R_4$: **X**; $R_5$:OH
**117.** $R_1$=$R_5$: $OCH_3$; $R_2$: $CH_3$; ; R=$R_3$=$R_4$: **X**
**118.** $R_1$: OH; $R_2$: $CH_3$; R=$R_3$=$R_4$: **X**; $R_5$:$OCH_3$
**119.** $R_1$=$R_5$: $OCH_3$; R=$R_2$=$R_3$=$R_4$: **X**
**120.** $R_1$= OH; R=$R_2$=$R_3$=$R_4$: **X**; $R_5$:$OCH_3$
**X.**

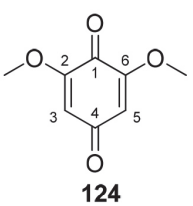


**121.** $R_1$: =O $R_2$: $CH_3$; $R_3$: **X**
**122.** $R_1$: OH $R_2$=$R_3$: **X**
**X.**

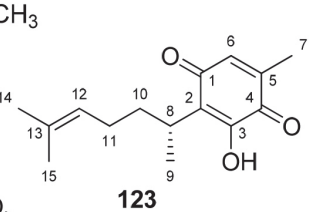


**114**





**124**



**123**

***Figure 2.*** *Compounds isolated from Helicteres species (cont.)*

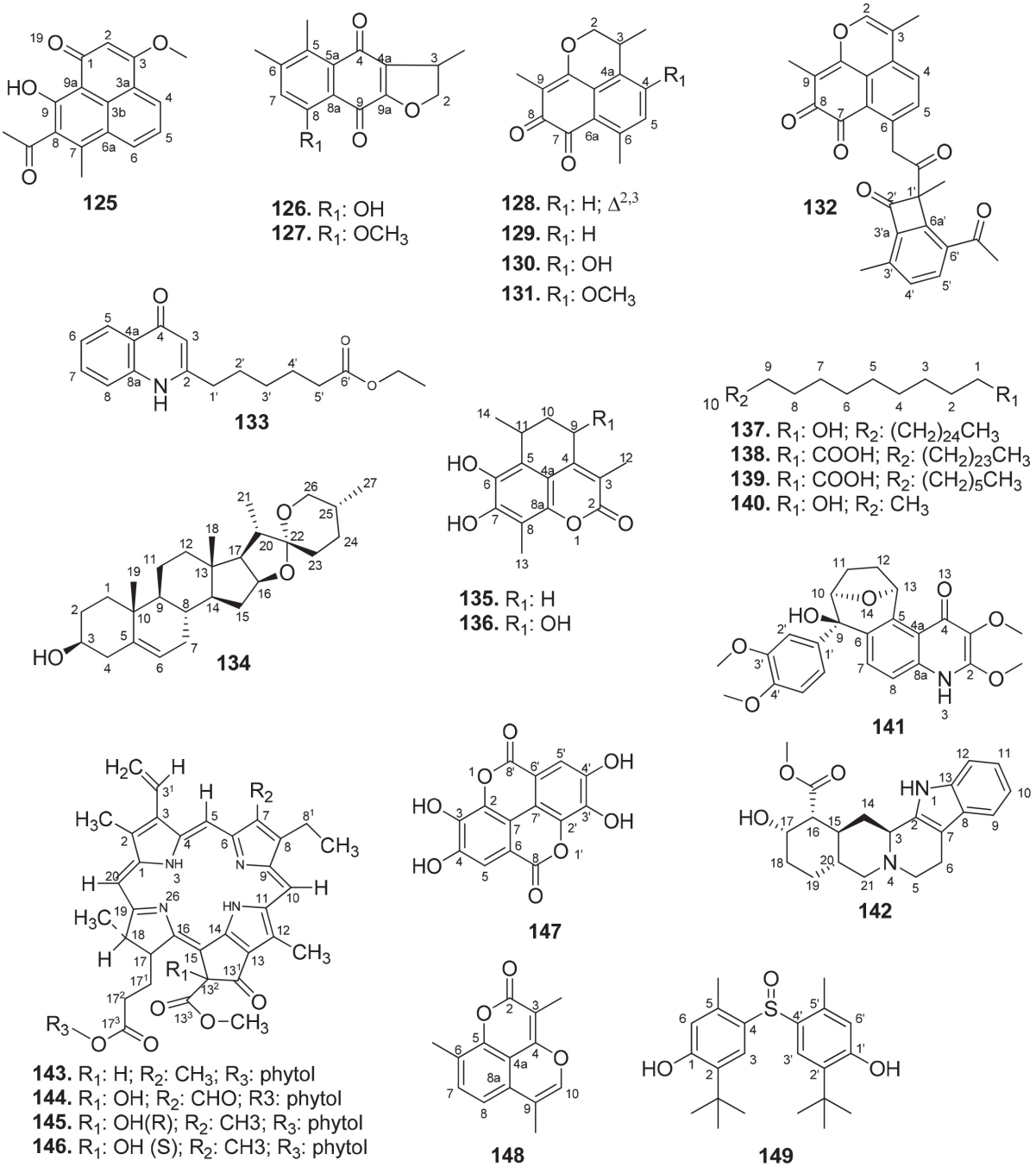



***Figure 2.*** *Compounds isolated from Helicteres species (cont.)*

*Anti-inflammatory and analgesic activity*

Natural products are widely used in folk medicine to treat inflammatory conditions, including fever, pain, migraine and arthritis, being targets for the development of new anti-inflammatory drugs.[172] Studies with plant extracts have shown promissory activity.[173]

*H. isora* root extract showed antinociceptive activity in mice.[101] *H. angustifolia* n-butanol fraction has anti-inflammatory and analgesic activity.[104] Non-clinical mice studies have showed through photoacoustic spectroscopy that *H. gardneriana* extract induces a significant reduction in the inflamed area.[106] Studies with extracts from the aerial parts of *H. hirsute* has been conducted in order to discover their mechanisms of action against inhibition of COX1 and COX2 *in vitro*[70] (Table 3).

*Antitumor and cytotoxic activity*

Cancer is one of the leading causes of mortality in the world. About 60% of current anticancer drugs are from natural origin, with emphasis on plant species that are rich in anticancer agents and can be used as an alternative to chemotherapeutic drugs as they are less toxic.[174] The effects of plant-derived natural products have been investigated to a large extent on cancer cell proliferation, survival, invasion and metastasis due to bioactivity and the diversity of their chemical constituents.[60,175]

*Helicteres* are used to decrease tumor progression by folk medicine. In order to evaluate this activity, extracts, fractions and isolated substances have been studied through the evaluation of cytotoxic activity mainly in liver, lung, colon and breast cancers (Table 3).

**Table 3.** *In vitro*, *in vivo*, *ex vivo* and *in silico* biological studies reported from *Helicteres* genus

| Species | Material used | Experimental model | Literature |
|---|---|---|---|
| | | **Anti-inflammatory and Analgesic Activity** | |
| ***H.i.*** | Roots extracts | *in vivo* – antinociceptive | 101 |
| ***H.a.*** | Ethyl acetate extract | *in vivo* – anti-inflammatory and antipyretic | 102,103 |
| ***H.a.*** | *n*-butanolic fraction | *in vivo* – anti-inflammatory and analgesic | 104 |
| ***H.h.*** | Aerial parts extract | *in vitro* – COX1/COX2 inhibition | 70 |
| ***H.ga.*** | Aerial parts ethanolic extract | *in vivo* – acute inflammation | 105 |
| ***H.ga.*** | Leaves ethanolic extract | *ex vivo* – topical use | 106 |
| | | **Antitumor and Cytotoxic Activity** | |
| ***H.i.*** | Fruits extract | *in vitro* – lung cancer | 107,108 |
| ***H.i.*** | Curcubitacin B and Isocurcubitacin B | not reported | 109 |
| ***H.i.*** | Stem hydroethanolic extract | *in vivo* – hepatocellular carcinoma | 110 |
| ***H.a.*** | Roots aqueous extract | *in vitro* – fibroblasts and osteosarcoma | 111 |
| ***H.a.*** | Triterpenes | *in vitro* – colorectal cancer | 60 |
| ***H.a.*** | Roots aqueous extract | *in vivo* – human fibrosarcoma | 25 |
| ***H.a.*** | Polysaccharides | *in vivo* – breast cancer | 112 |
| ***H.a.*** | 2, 3, 3 β-*O*-[(E)-coumaroyl] betulinic acid and pyracrenic acid | *in vitro* – colorectal cancer | 44 |
| ***H.a.*** | Roots ethanolic and aqueous extract | *in vitro* – cell lines of lung cancer, colon and hepatocellular carcinoma | 25,111 |
| ***H.a.*** | Roots aqueous extract | *in vitro* – osteosarcoma and *in vivo* – pulmonary metastasis and subcutaneous xenograft | 113 |
| ***H.a.*** | Curcubitacin B and J | *in vitro* – hepatocellular carcinoma and malignant carcinoma | 51 |
| ***H.h.*** | (+/-)-pinoresinol | *in vitro* – lung and breast cancer | 46 |
| ***H.h.*** | Roots extract | *in vitro* – human KB cell lines | 114 |
| ***H.veg.*** | Leaves extract | *in vitro* – *Salmonella typhimurium* | 47 |
| ***H.s.*** | Leaves hydroethanolic extract | *in vivo* – ovarian cancer cell lineages | 8 |
| | | **Hepatoprotective Activity** | |
| ***H.i.*** | Bark aqueous extract | *in vivo* – changes in liver enzymes | 115 |
| ***H.i.*** | Bark ethanolic extract | *in vivo* – changes in liver enzymes | 116-118 |
| ***H.a.*** | Aqueous extract | *in vivo* – inhibits hepatic fibrosis | 119 |
| ***H.a.*** | Methyl helicterate | *in vivo* – inhibits hepatic fibrosis | 120,121 |
| | | **Antidiabetic and Hypolipidemic Activity** | |
| ***H.i.*** | Roots ethanolic extract | *in vivo* – sensitizing and hypolipidemic insulin | 122 |
| ***H.i.*** | *n*-butanolic fraction | *in vivo* – maintain normal glycemic levels | 123 |
| ***H.i.*** | Bark aqueous extract | *in vivo* – reduced blood glucose levels | 30 |
| ***H.i.*** | Bark aqueous extract | *in vivo* – reduction of peroxidation products | 32 |
| ***H.i.*** | Roots *n*-butanolic extract | *in vivo* – reduced glucose and total cholesterol | 124 |
| ***H.i.*** | Bark aqueous extract | *in vivo* – reduction of cholesterol, free fatty acids and triglycerides | 31 |
| ***H.i.*** | *n*-butanolic extract | *in vivo* – hypoglycemia | 125 |
| ***H.i.*** | Fraction rich in saponin | *in vivo* – decreased serum levels of lipids and glucose | 126 |
| ***H.i.*** | Stem extract | *in vivo* – glycogen and carbohydrate metabolism | 127 |
| ***H.i.*** | Bark aqueous extract | *in vivo* – decreased glucose levels | 128 |
| ***H.i.*** | Bark aqueous extract | *in vivo* – total blood glucose and lipids | 127 |
| ***H.i.*** | Fruits aqueous extract | *in vitro* – glucose uptake | 129 |
| ***H.i.*** | Fraction rich in saponin | *in vitro* – increases glycogen synthesis | 130 |
| ***H.i.*** | Fruits ethanolic extract | *in vivo* – stabilizes lipids levels | 122 |
| ***H.i.*** | Roots hydroethanolic extract and roots *n*-butanolic extract | *in vivo* – reduced glycemia, total cholesterol, triglycerides and urea | 34 |
| ***H.i.*** | Fruits aqueous extract | *in vivo* – increases glucose uptake and transport | 131 |
| ***H.i.*** | Stem extract | *in vivo* – normalizes glucose, urea and creatinine levels | 88,116 |
| ***H.i.*** | Bark aqueous extract | *in vivo* – antiperoxidative activity | 88 |
| ***H.i.*** | Isolated constituents | *in silico* – insulin receptors | 79 |
| ***H.i.*** | Roots extract | *in vivo* – reduction of plasma glycoproteins | 132,133 |
| ***H.i.*** | Roots extract | *in vivo* and *in vitro* – inhibition of α-amylase and reduction of glutathione | 134,135 |
| ***H.i.*** | Fruits aqueous extract | *in vivo* – hypoglycemia in patients with type II diabetes | 22 |
| ***H.i.*** | *n*-butanolic extract | *in vivo* – regulates blood glucose levels | 136 |
| ***H.i.*** | Fruits ethanolic extract | *in vivo* – regulates blood glucose levels | 137 |

**Table 3.** *In vitro*, *in vivo*, *ex vivo* and *in silico* biological studies reported from *Helicteres* genus (cont.)

| Species | Material used | Experimental model | Literature |
|---|---|---|---|
| ***H.a.*** | Roots aqueous extract | *in vivo* – increases glucose uptake | 138 |
| ***H.a.*** | Roots ethanolic extract | *in vivo* – increases the uptake of glucose and adipocytes | 139 |
| ***H.a.*** | - | *in vivo* – inhibition of α-glicosidase | 138,139 |
| | | **Antioxidant Activity** | |
| ***H.i.*** | Bark aqueous extract | *in vitro* – inhibition of peroxidation radicals | 81 |
| ***H.i.*** | Fruit hot aqueous extract | *in vitro* – inhibition of radicals $H_2O_2$ and NO | 27 |
| ***H.i.*** | Fruits phenolic extracts | *in vitro* – inhibition of radicals ABTS, Hydroxyl and DPPH | 140 |
| ***H.i.*** | Fruits aqueous extract | *in vitro* – inhibition of radicals DPPH and TBARS | 129 |
| ***H.i.*** | Fruits aqueous extract | *in vitro* – inhibition of radicals Hydroxyl, $H_2O_2$ and DPPH | 141 |
| ***H.i.*** | Fruits extract | *in vitro* – inhibition of radicals DPPH | 107 |
| ***H.i.*** | Fruits extract | *in vitro* – inhibition of radicals FRAP and DPPH | 142,143 |
| ***H.i.*** | Fruits extract | *in vitro* – inhibition of radicals DPPH and $H_2O_2$ | 107 |
| ***H.i.*** | Fruits and barks extracts | *in vitro* – inhibition of lipid peroxidation | 142 |
| ***H.i.*** | Roots aqueous extract | *in vitro* – inhibition of radicals ABTS and DPPH | 144 |
| ***H.i.*** | Leaves, barks, roots and fruits extracts | *in vitro* – inhibition of radicals FRAP and DPPH | 145 |
| ***H.i.*** | Leaves and fruits extracts | *in vitro* – inhibition of radical DPPH | 146 |
| ***H.a.*** | Polysaccharides | *in vitro* – inhibition of radicals ABTS, Hydroxyl and DPPH | 147-149 |
| ***H.a.*** | Roots ethanolic and aqueous fractions | *in vitro* – inhibition of ABTS and DPPH | 150 |
| ***H.h.*** | Leaves extracts | *in vitro* – inhibition of radicals ABTS, DPPH and FRAP | 148 |
| ***H.h.*** | Fraction rich in saponin | *in vitro* – inhibition of radicals ABTS, DPPH, FRAP and CUPRAC | 24,45,95,111, 151 |
| ***H.h.*** | Stem and Leaves extracts | *in vitro* – inhibition of radicals, ABTS, DPPH and FRAP | 45,95,96 |
| ***H.veg.*** | Stem extracts | *in vitro* – inhibition of radicals, ABTS and DPPH | 47 |
| | | **Antimicrobial and Antiviral Activity** | |
| ***H.i.*** | Fruits extracts | *in vitro – E. coli*, *Staphylococcus epidermidis*, *Salmonella typhimurium* and *Proteus vulgaris* | 152 |
| ***H.i.*** | Fruits acetone extracts | *in vitro – Enterococcus faecalis*, *Escherichia coli* and *Bacillus cereus* | 153 |
| ***H.i.*** | Leaves ethanolic extract | *in vitro – Escherichia coli*, *Steptococcus* and *Salmonella* | 154 |
| ***H.i.*** | Leaves and fruits extracts | *in vitro – Staphylococcus aureus*, *Bacillus subtilis* and *B. coagulans*; *Escherichia coli*, *Pseudomonas aeruginosa* and *Salmonella typhi*; *Bipolaris sorokiniana*, *Fusarium oxysporum* f.sp. *zingiberi*, *Colletotrichum capsici* and *Curvularia* sp. | 150 |
| ***H.i.*** | Stem and leaves extracts | *in vitro – E. coli*, *Pseudomonas*, *S. aureus*, *Bacillus subtillis*, *Aspergillus fumigatous*, *Aspergillus awamori*, *Rhizopus oryzae*, *Tricoderma viridae* and *Culmularia oryzae* | 155 |
| ***H.i.*** | Fruits aqueous extract | *in vitro – Pseudomonas aeruginosa* | 156 |
| ***H.i.*** | Oleanolic acid | *in vitro – S. aureus*, *E coli*, *P. aeruginosa*, *B. cereus* and *A. flavus* | 88 |
| ***H.i.*** | β-sitosterol | *in vitro – E. coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Bacillus cereus* | 88 |
| ***H.i.*** | Barks and stems extracts | *in vitro – Cryptococcus neoformans*, *Candida tropicalis*, *Trychophyton rubrum*, *Microsporum furfure* and *Epidermophyton floccosum* | 157 |
| ***H.i.*** | Roots hydroethanolic extract | *in vitro – Bacillus subtilis*; *Micrococcus luteus*; *S. aureus*; *E. coli*; *P. vulgaris*; *P. aeruginosa*; *S. typhimurium*; *A. niger*; *C. albicans* and *S. cerevisiae* | 101 |
| ***H.i.*** | Fruits, barks and leaves extracts | *in vitro – Escherichia coli*, *Salmonella typhii*, *Staphylococcus aureus*, *Corynebacteria diphtheriae* and *Nocardia* sp. | 158 |
| ***H.i.*** | Leaves ethanolic extract | *in vitro – Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Aspergillus niger* | 159 |
| ***H.i.*** | Fruits methanolic extract | *in vitro – Candida albicans* | 148 |
| ***H.i.*** | 10-methyl, 4-isopropenyl, dodecahydro- ethanophenanthrene | not reported | 65 |
| ***H.a.*** | not reported | *in vitro – E. coli* | 160 |
| ***H.a.*** | Triterpenes | *in vivo* and *in vitro* – Hepatitis B | 161 |
| ***H.a.*** | Methyl helicterate | *in vivo* and *in vitro* – anti HBV | 162,163 |
| ***H.h.*** | Roots extract | *in vitro – Staphylococcus aureus* and *Lactobacillus fermentum* | 114 |
| ***H.h.*** | Saponin-enriched fractions | *in vitro – E. coli* and *S. lugdunensis* | 164 |
| ***H.gr*** | Aerial parts extract | *in vitro – Bacillus subtilis*; *Micrococcus luteus*; *Enterobacter cloacae*; *Acinetobacter calcoaceticus*; *Aspergilus oryzae*; *Curvularia luneta*; *Mucor* sp. | 165 |

**Table 3.** *In vitro*, *in vivo*, *ex vivo* and *in silico* biological studies reported from *Helicteres* genus (cont.)

| Species | Material used | Experimental model | Literature |
|---|---|---|---|
| | | **Other Activities** | |
| ***H.i.*** | Fruits extract | *in vitro* and *in vivo* – antispasmodic | 37 |
| ***H.i.*** | Fruits extract | *in vitro* – cardiotonics | 166 |
| ***H.i.*** | Fruits aqueous extract | *in vivo* – anthelminthic | 167 |
| ***H.i.*** | Fruits extract | *in vivo* – anthelminthic | 144 |
| ***H.i.*** | Bark methanolic extract | *in vitro* – cytoprotectors | 168 |
| ***H.i.*** | Bark aqueous extract | *in vivo* – acute oral toxicity | 39 |
| ***H.i.*** | 10-methyl, 4-isopropenyl, dodecahydro- ethanophenanthrene | *in vivo* – antispasmodic | 65 |
| ***H.i.*** | Fruit extract | Demulcent and Astringent | 169 |
| ***H.a.*** | Terpenoids | *in silico* – ulcerative cults | 170,171 |
| ***H.a.*** | Leaves hydroethanolic extract | *in vivo* – acute and subchronic toxicity | 8 |
| ***H.vel.*** | Aerial parts extract | *in vitro* – Larvicidal activity against *Aedes aegypti* | 12 |
| ***H.vel.*** | Tiliroside and 7,4′-di-*O*-methyl-8-*O*-sulphate flavone | *in silico* and *in vitro* – Larvicidal activity against *Aedes aegypti* | 89 |
| ***H.s.*** | Hydroethanolic extract | *in vivo* – gastroprotective | 8 |
| ***H.s.*** | Hydroethanolic extract | *in vivo* – acute and subchronic oral toxicity | 8 |
| ***H.e.*** | Aerial parts extract | *in vitro* – Larvicidal activity against *Aedes aegypti* | 48 |
| ***H.veg*** | Leaves and stem extracts | *in vitro* – *Artemia salina* eggs | 47 |

***H.i.*: *H. isora*; ***H.a.*: *H. angustifolia*; ***H.vel.*: *H. velutina*; ***H.h.*: *H. hirsuta*; ***H.veg.*: *H. vegae*; ***H.s.*: *H. sacarolha*; ***H.ga.*: *H. gardineriana*; ***H.e.*: *H. eichleri*; ***H.gr*: *H. grazumifolia*.**

The acetone extract of *H. isora* fruits exhibited better cytotoxic activity *in vitro* against lung cancer cells.[107] Studies with the terpenes Helicteric acid (**38**), oleanolic acid (**45**) and betulinic acid (**12**) isolated from *H. angustifolia* have shown important anticancer activity and showed that compounds could decrease proliferation and induce apoptosis in HT-29 colorectal cancer cells *in vitro*.[60] A similar activity was developed by the compounds 2, 3, 3 β-*O*-[(*E*)-coumaroyl] betulinic acid (**15**) and pyracrenic acid (**16**).[44]

*In vivo* studies revealed that hydroethanolic extract flavonoid-rich of *H. sacarolha* and phenolic compounds have good activity in ovarian cancer cell lineages, being non-toxic when ingested orally,[8] while hidroethanolic stem bark extract of *H. isora* shows activity against hepatocellular carcinoma in mice.[167]

*Hepatoprotective activity*

Extracts of several plant species have shown hepatoprotective activity[176-178] and approximately 100 of these species have been used in the preparation of over 700 herbal formulations that are available for use in prevention and treatment of liver disease.[179,180]

The hepatic protection exerted by the *H. isora* and *H. angustifolia* species was also investigated *in vivo*, where the main parameters of alterations in liver enzymes production and serum markers are evaluated. *H. isora* bark ethanolic extract and *H. angustifolia* water extract demonstrated hepatoprotective activity against carbon tetrachloride induced liver damage in rats and mice, respectively.[116] The methyl helicterate (**30**) isolated from *H. angustifolia* acts on carbon tetrachloride in induced hepatic fibrosis of rats, which may be associated with its free radical scavenging action and antioxidant activity. Another proposed mechanism of action of this substance would be the inhibits activation of hepatic stellate cells, modulating apoptosis and autophagy.[120,121]

*Antidiabetic and hypolipidemic activity*

Available literature shows that various chemical compounds with antidiabetic properties have been identified in some plant species,[181,182] among which we can highlight some belonging to the *Helicteres* genus.

The ethanolic extract of *H. isora* roots causes significant reduction in glucose, triglyceride and insulin levels in mouse plasma, suggesting that it has insulin sensitizing and hypolipidemic activity with potential use in the treatment of type 2 diabetes.[28] Researches over this species have also proven the antidiabetic activity of the aqueous extracts of its peels, stem and fruits.[30,127,129]

The extract and n-butanolic fractions of *H. isora* have shown good *in vivo* activity with antihyperglycemic activity, reducing glucose and total cholesterol levels.[123,124] Saponin-rich fractions also exhibit this activity *in vitro* and *in vivo*.[126,130] Molecular docking with insulin receptors was analyzed with compounds isolated from *H. isora* fruits,[183] and the results suggested that they may be useful for treating diabetes.

*H. angustifolia* roots aqueous and ethanolic extracts have also shown significant antidiabetic activity *in vivo*, significant alpha-glucosidase inhibitory and moderate enhanced glucose consumption activity, while having low cytotoxicity and acute toxicity.[138,139]

*Antioxidant activity*

Antioxidants are important for preventing human diseases. Naturally occurring antioxidants such as ascorbic acid, vitamin E and phenolic compounds can reduce the oxidative damage associated with various diseases including cancer, cardiovascular disease, cataract, atherosclerosis, diabetes, arthritis, immune deficiency diseases and aging.[27]

Evaluation of antioxidant activity of the species *H. isora*, *H. angustifolia*, *H. hirsuta* and *H. vegae*, mainly with respect to fruit extract,[141] rich fractions of saponins[24] and polissacarids,[147] showed that they are capable of inhibiting *in vitro* peroxidation radicals such as DPPH (1,1-diphenyl-2-picryl-hydrazyl), $H_2O_2$ (Hydrogen peroxide), NO (Nitric Oxide), ABTS (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid)), TBARS (thiobarbituric acid-reactive substances), FRAP (ferric reducing antioxidant power) and CUPRAC (cupric reducing antioxidant capacity).

*Antimicrobial and antiviral activity*

In the current scenario, due to the various pathogenic microorganisms, infectious diseases are still one of the leading reasons behind the worldwide death rates.[184] The emergence of

multiple commonly used antibiotic drug resistant bacteria is a severe health problem and major challenge for global drug discovery programs,[154] and the use of plant extracts and isolated compounds with known antimicrobial properties becomes an important alternative in therapeutic treatments.[185]

*H. isora* and *H. angustifolia* organic extracts have been extensively studied for their potential to act as antimicrobial agents.[150] Among the isolated compounds, oleanolic acid (**45**)[88] and β-sitosterol (**51**)[88] showed good antibacterial activity, while methyl helicterilate compound (**49**) showed potential antiviral activity[162] (Table 3).

*Other activities*

Other activities have been reported from *Helicteres* species. *H. isora* stems aqueous extract showed no toxicity when administered orally at concentrations of 100 and 200 mg/kg in rats.[39] Researchers also evaluate antispasmodic,[37] gastroprotective,[8] anthelmintic[167] and larvicide against *Aedes aegypti* larvae[12,48] activities, among others. In addition, studies were also carried out to evaluate the nutritional value of *H. isora* fruits and stems.[186]

## CONCLUSIONS

*Helicteres* L. is one of the genera belonging to Sterculiaceae clade in Malvaceae family with several notable activities. Previous studies have revealed that terpenoids, flavonoids and lignoids are the dominant constituents of *Helicteres* species. However, information about this genus is scarce and not systematic. The *in vitro* and *in vivo* studies carried out to date prove traditional medicine reports regarding the activities of those species. However, pharmacological tests with isolated substances are still rare from this genus and its compounds, especially those unpublished in the literature, resulting in unexplored potentials.

Given the presented data, it is extremely important to continue exploring the chemical and biological potentials of these and other species present in the American and Asian flora, considering the need to find substances with biological activities that may be used for mankind benefit.

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