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Phytochemical, Pharmacological and Toxical Properties of *Euphorbia Helioscopia*: Review

Anjoud Harmouzi^{1,2*}, Yassine El Ammari¹, Amina CHLOUCHI¹, Rabha AFROUKH¹, Ahmed Boughdad²

¹Agrophysiology, Biotechnology, Environment and Quality laboratory, Sciences Faculty, Ibn Tofail University, BP 133, 14000 Kenitra. Morocco

²Department of Plant Protection and Environment. National School of Agriculture - Meknes. B.P. S/40 50000; Meknes, Morocco

*Corresponding author: Anjoud Harmouzi, Agrophysiology, Biotechnology, Environment and Quality laboratory, Sciences Faculty, Ibn Tofail University, BP 133, 14000 Kenitra. Morocco, E-mail: nojoud.harmouzi@gmail.com

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ABSTRACT

Euphorbia helioscopia L. (Euphorbiaceae), also known as "Sun spurge" is one of used herbs in most parts of the world since thousands of years. This work aims to provide updated comprehensive and categorized information on chemical composition, pharmacological and toxic properties of this plant. To achieve this purpose, several scientific databases were used, including Wiley, PubMed, Web of Science, Springer, Science Direct, Elsevier, and Google Scholar and related books published up to December 2019 were also used as references. After description of its history, botanical characteristics and distribution, this review highlights the different types of secondary metabolites, such as diterpenoids, tannins, glucosides and steroids, which have been isolated from *E. helioscopia* L. in several researches over the last four decades. Related Twenty five pharmacological activities (among them: antibacterial, antiviral, antioxidant, antifungal, phytotoxic, anthelmintic, antitumor, anti-allergic, anti-asthmatic, cytotoxic, anticancer, allelopathic, anti-nociceptive, anti-inflammatory, anti-pyretic, vasodepressor, antileishmanial, lipid-lowering activity, and triglyceride-lowering activity) are presented and discussed. *E. helioscopia* L. toxicity related studies against Humans, snails and some herbs are summarised and presented with correspondent references. This study can be used by researches interested by this plant since it resumes all relevant published papers in link with *E. helioscopia* L.

Keywords: *Euphorbia Helioscopia*; Chemical composition; Pharmacological properties; Toxicity

INTRODUCTION

Euphorbiaceae is the largest family of Anthophyta with 300 genera and 5,000 species [1]. Euphorbia, is one of the largest angiosperms' genera, with about 2,000 species, and has long been known for its wide variety of growth forms, including many xerophytic species. Despite its great vegetative diversity, the genus is morphological united by the possession of a cyathium which is a very small inflorescence that looks like a single flower [1-3].

Euphorbia helioscopia L., also called Sun spurge, is an annual plant with a tall between 10 and 50 cm high, with a rich latex stem, oval alternate leaves and small yellow-green flowers. The plant is native to temperate regions of Eurasia but has been adapted to subtropical conditions. It behaves as a winter annual in Japan that is blooming from April to May. In Morocco, this plant blooms from December to April in plains and up to May in mountainous areas [4]. Most *E. helioscopia* L. compounds are biologically active; for example: Antibacterial [1, 5-8], antitumor/anticancer [9-12] antioxidant [1, 13-15], Antifungal [16] plus other types of activities. Plants in Euphorbiaceae family are also promising sources of high quality tanning agents for leather industry [17]. *E. helioscopia* L. has been considered as a medicinal plant and is used in traditional medicine in various countries of the world [3, 18-20]. For Maghrebian traditional medicine, *E. helioscopia* L. is locally called "Bou Labeena" (in reference to the plant's milky latex). However, *Euphorbia* stems are an irritant drug that cause severe toxicity like phytotoxic effects [21], Molluscicidal activity [22-24] and skin irritant [25].

The objective of this review is to present an evaluation of art state of *E. helioscopia* L., in particular chemical compounds identified and characterized in its different parts, in one hand; in the other hand, to examine pharmacological and toxic properties of this plant, based on a comprehensive and in-depth analysis of relevant literature.

MATERIALS AND METHODS

In this work we collected literatures published documents up to December 2019 on phytochemistry, botany, pharmacology and toxicity of *E. helioscopia* L. All available information on this plant was retrieved by Internet databases (Springer, PubMed, Web of Science, Wiley, Science Direct, Elsevier, and Google Scholar) and a number of books and PhD dissertations were also used. Used key words in the search were: "*Euphorbia helioscopia* L.", "Traditional uses of *Euphorbia helioscopia* L.", "Chemical composition of *Euphorbia helioscopia* L.", "pharmacological activity", "toxicity". Scientific name of the plant has been identified and validated by the Scientific Institute of Rabat (Morocco) and through www.theplantlist.org.

Traditional uses of *Euphorbia* L. (*Euphorbiaceae*)

Historically, natural extract from plants have showed a significant role in humans live, whether for food or for drugs [26]. *Euphorbia* L. (*Euphorbiaceae*) has attracted human interest around the world since the earliest and even prehistoric times [27-29]. *Euphorbia* species are easily identified especially by their milky latex and unique inflorescences (cyathia) [30]. They are known for their use as ornamental and domestic plants [31], and their latex has contributed to the economic interest for certain species such as *Euphorbia antisyphilitica* Zucc [31] and *Euphorbia Intisy Drake* (intisy rubber) [31]. According to Hippocrates, Galen and Dioscorides [32, 33], Sumerians and Akkadians knew the toxic properties of *E. helioscopia* L. [34], the medicinal properties of "euphorbium" (gum from *E. resinifera* Berg [32] and the presence of active natural products in the latex [35,36]. In 1752 Carl Linnaeus presented *Euphorbia* genus with various medicinal uses, including topical treatments and purging of the gastrointestinal tract [37-39]. *E. helioscopia* L. takes her name from a Greek origin, deriving from "helioscopion" used first by Dioscorides to describe this species and meaning "sun gazer". In fact, according to the Roman naturalist Pliny, the plant moves its flowers round to follow the sunlight [40, 41]. Furthermore, as reported for other species belonging to the *Euphorbiae* genus, the plant was used by Greeks and Romans to take away all kinds of warts, knobs, and the hard calluses of fistulas, hot swelling and carbonucles. Nowadays, the plant is still used in China for a variety of ailments: as a cure for boils, to get rid of worms, and to bring down high temperatures [41].

Botanical characteristics

E. helioscopia L. (Figure 1) is a fleshy annual plant, glossy green and glabrous, up to 50 cm tall but more commonly between 10 to 30 cm. All parts of the plant emit a milky sap, once cut. *E. helioscopia* L.'s stems are clearly tinged with red and radiate outward from a central point. All leaves (1 to 2 mm long) are usually attached directly to the stem and do not appear on petioles. Not very visible, light green to pale yellow, inflorescences (cyathias) occur at stems' ends and have 4 lobes. Each lobe has a round yellowish gland [42, 43].



Figure 1: *Euphorbia helioscopia* L. (By Anjoud HARMOUZI)

E. helioscopia L. is classified in reign: Plantae, under reign: *Tracheobionta*, Super division: *Spermatophyta*, Division: *Magnoliophyta*, Class: *Magnoliopsida*, Subclass: *Rosidae*, Order: *Malpighiales*, Family *Euphorbiaceae*, Genus: *Euphorbia* and Species: *Euphorbia helioscopia* [43].

Distribution

Euphorbia helioscopia is native to North Africa, Europe, and some parts of Asia. It was introduced in North and South America as shown in the cart below (Figure 2). African native countries are Algeria, Egypt, Libya, Morocco and Tunisia, European ones are: Albania, Belgium, Bulgaria, Cyprus, Czech, Finland, France, Germany, Great Britain, Greece, Hungary, Ireland, Italy, Netherlands, Norway, Poland, Portugal, Romania. Asian ones are: Afghanistan, Bangladesh, Belarus, China, India, Iran, Iraq, Japan, Kazakhstan, Kirgizstan, South Korea, Lebanon, Syria, Mongolia, Pakistan, Palestine, Saudi Arabia, Tadzhikistan, Taiwan, Turkey, Turkmenistan and Vietnam. While introduced countries are: Canada, United States of America and Argentina [44-52].

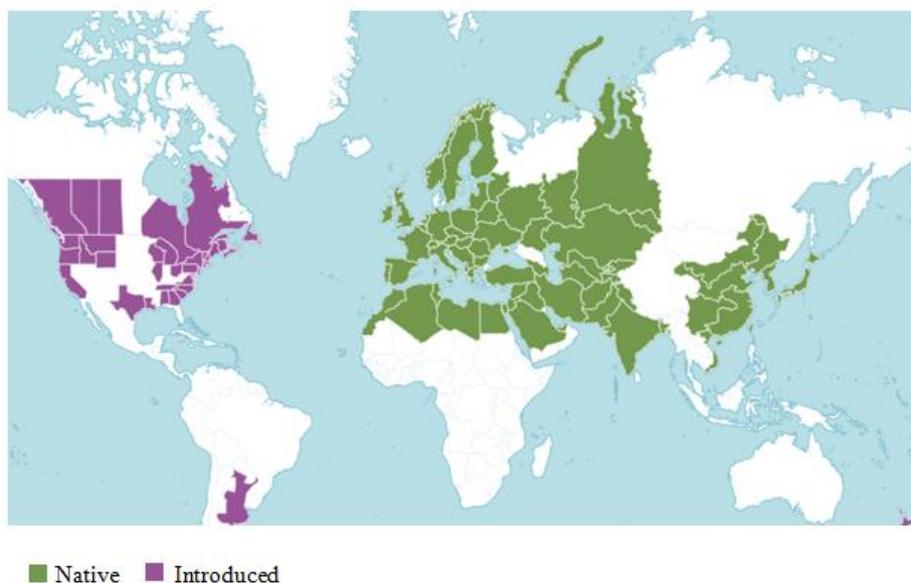


Figure 2: Distribution of *Euphorbia helioscopia* L. (<https://www.ipni.org/n/346754-1>)

Chemical composition

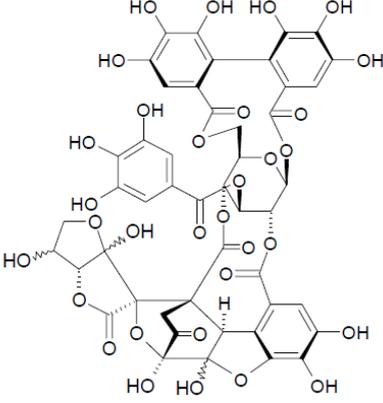
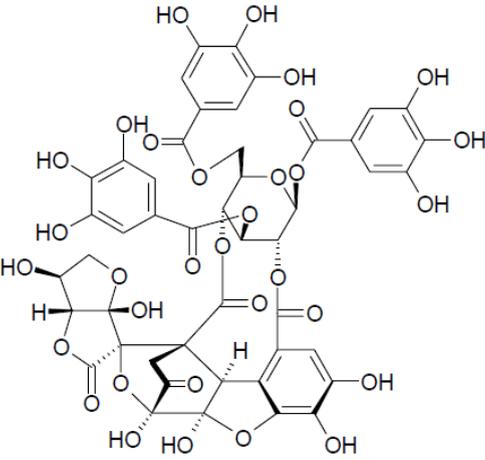
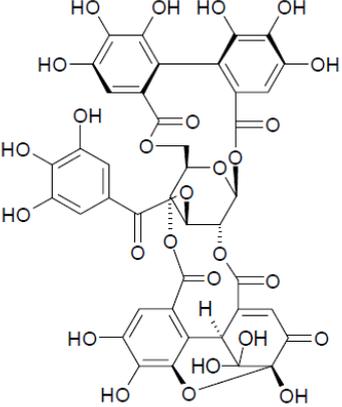
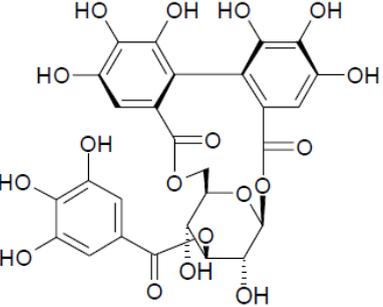
Euphorbia is the largest genus of *Euphorbiaceae* family, which is well known for the chemical diversity of terpenoids [35]. Diterpenoids are particularly rich and diversified in *Euphorbia* species, with more than 650 diterpenoids that have been isolated and identified, including jatrophanes, lathyranes, ingenanes, tiglianens, abietanes, kauranes, pimaranes, daphnanes, casbbanes and myrsinanes [35- 36, 53]. A large number of secondary metabolites have been reported from *E. helioscopia* L. plant including diterpenoid, triterpenoid, tannins, glucosides and lipids [3,54-59] which offer to *E. helioscopia* L. a wide array of bioactive functions.

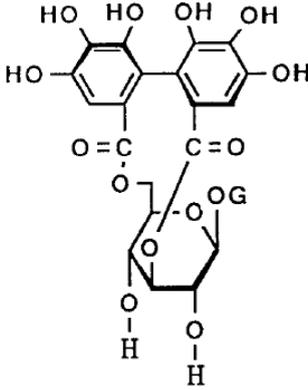
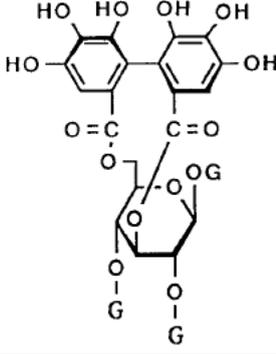
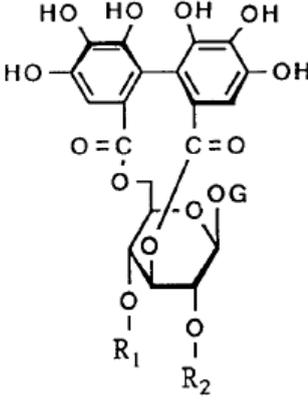
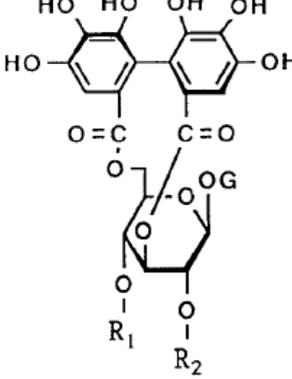
More than 133 diterpenoids have been isolated and structurally characterized from *E. helioscopia* L. [57, 60], which present the main class components studied in this plant (table 1), e.g Euphohelin A [61], Euphornin A-K (1-11), Euphoscopin A-L, Euphorpin A- F [62], Euphorbiapene A-D [63, 62] and Helioscopianoids A-Q [64].

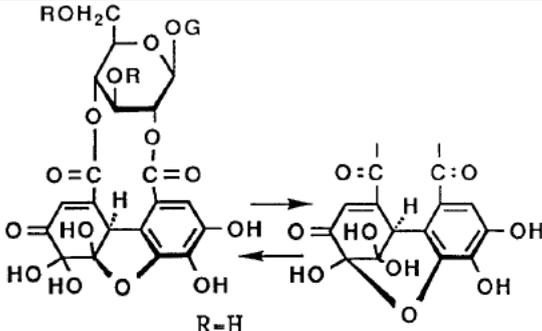
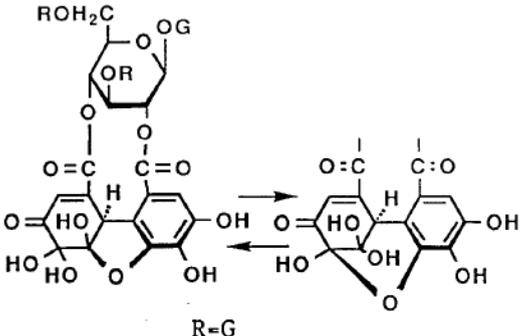
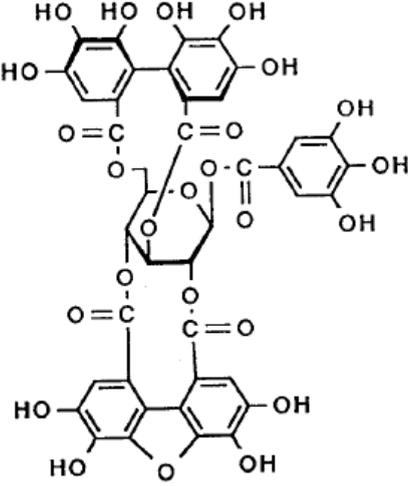
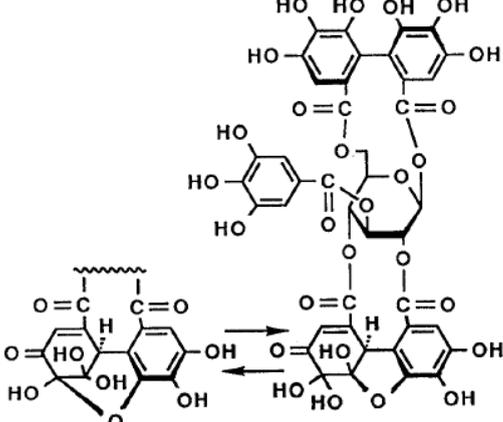
Oil content of *Euphorbia helioscopia*'s seeds is equal to 30.33 % with a d15: 0.9346, nD: 1.4847, Iodine index, % J2: 176.6–204.4, and saponification value is 191.1mg KOH [65]. According to [64], *E. helioscopia* L. contains diterpenoid esters of jatrophane, helioscopianoides A–Q and euphornin N [66-67, 115]. Triterpenes like Euphorbatrine A-G [68]. Four hydrolysable tannins named: helioscopinins A & B, and helioscopins A & B were found in all parts of *E. helioscopia* L. [55-17, 69]. Other studies have revealed the presence of flavonoids like, Heliosin [70,71], glycosides such as quercetin-3-pglucoside, quercetin-3-β-galactoside, quercetin-3-β-galactoside-2"-galla [72] and aryl glycoside, 300-O-galloyl-benzyl-O-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside [57-73,74], Hyperoside and Quercetin [75], steroids and lipids like Glucoclionasterol [54, 59] and other secondary metabolites such as 24-methylene cycloartanol, 24-methylenecycloart-3-one, cycloartanol, and stigmast-4-ene-3-one [3]. Diversity in secondary metabolites in all parts of *E. helioscopia* L. would explain their various uses in several areas.

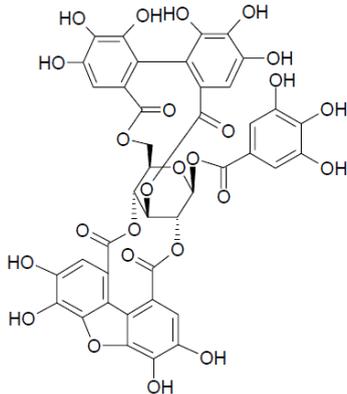
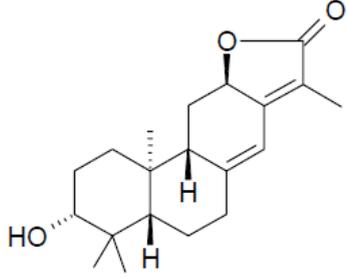
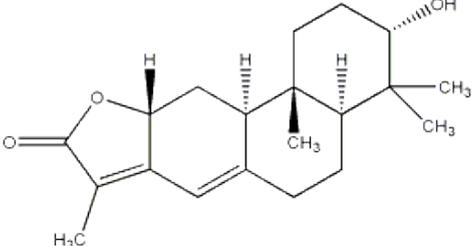
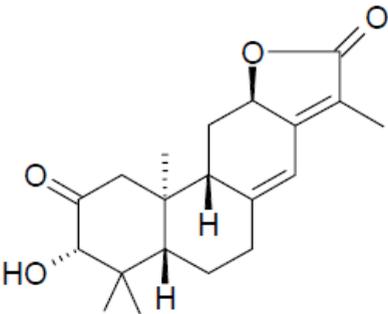
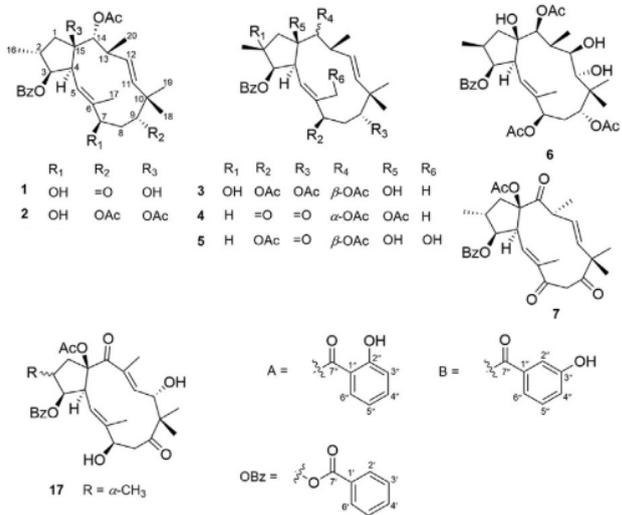
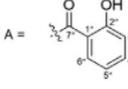
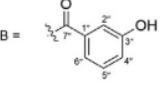
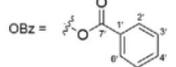
Details related to extraction methods used can be found in mentioned references. Throughout this review, it is seen that chemical proprieties are deeply investigated by researchers from different countries from 1968 up to nowadays (2019). Some substances are present in all parts of the plant while other are located in some of them (table3). Further studies about the use of these chemical constituents can be envisaged. *E. helioscopia* L. diterpenoids have been extensively studied over the years. However, for many other classes of compounds, with have nteresting pharmacological affects possibilities, investigations are scarce. Examples of these compounds include saponins especially in *E. helioscopia* L. roots, and tannins isolated from *E. helioscopia* L. where there is still much to be explored and published.

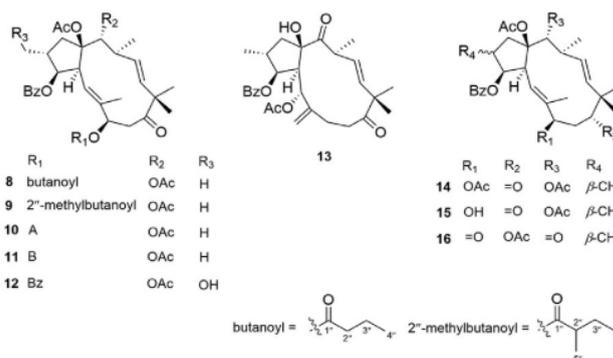
Table 1: Identification of the main chemical constituents in *Euphorbia helioscopia* L.

Compound class	Compound name and formula	Chemical structure	References
Tannins	Helioscopin A $C_{47}H_{34}O_{32}$		[17-55,69]
	Helioscopin B $C_{47}H_{36}O_{32}$		[17-55,69]
	Helioscopinin A $C_{41}H_{28}O_{27}$		[17-55-69, 76]
	Helioscopinin B $C_{27}H_{22}O_{18}$		[17-55,69]

<p>Corilagin C₂₇H₂₂O₁₈</p>		[55]
<p>Punicafolin C₄₁H₃₀O₂₆</p>		[55]
<p>Geraniin C₄₁H₂₈O₂₇</p>	 <p style="text-align: center;">$R_1, R_2 = (R)DHHDP$</p>	[55]
<p>Elaeocarpusin C₄₇H₃₄O₃₂</p>	 <p style="text-align: center;">$R_1, R_2 = (R)EC$</p>	[55]

<p>Furosin C₂₇H₂₂O₁₉</p>	 <p>R=H</p>	[55]
<p>Terchebin C₄₁H₃₀O₂₇</p>	 <p>R=G</p>	[55]
<p>Mallotusin C₄₁H₂₆O₂₅</p>		[55]
<p>Carpinusin C₄₁H₃₀O₂₇</p>		[55]

	<p>Mauotusinin C₄₁H₂₆O₂₅</p>		<p>[55]</p>
<p>Diterpenoids</p>	<p>Helioscopinolide A C₂₀H₂₈O₃</p>		<p>[69]</p>
	<p>Helioscopinolide B C₂₀H₂₈O₃</p>		<p>[69]</p>
	<p>Helioscopinolide C C₂₀H₂₆O₄</p>		<p>[69]</p>
	<p>Helioscopianoids A–Q 1: C₂₉H₃₈O₇Na 2: C₃₃H₄₄O₉Na 3: C₃₃H₄₄O₁₀Na 4: C₃₁H₃₈O₈Na 5: C₃₁H₄₀O₉Na 6: C₃₃H₄₆O₁₁Na 7: C₂₉H₃₄O₇Na 8: C₃₅H₄₆O₉Na 9: C₃₆H₄₈O₉Na 10: C₃₈H₄₄O₁₀Na 11: C₃₈H₄₄O₁₀Na 12: C₃₈H₄₄O₁₀Na 13: C₂₉H₃₆O₇Na 14: C₃₃H₄₂O₉Na 15: C₃₁H₄₀O₈Na 16: C₃₁H₃₈O₈Na 17: C₂₉H₃₆O₈Na</p>	 <p> R_1 R_2 R_3 R_1 R_2 R_3 R_4 R_5 R_6 1 OH =O OH 3 OH OAc OAc β-OAc OH H 2 OH OAc OAc 4 H =O =O α-OAc OAc H 5 H OAc =O β-OAc OH OH </p> <p> A =  B =  OBz =  </p>	<p>[64]</p>

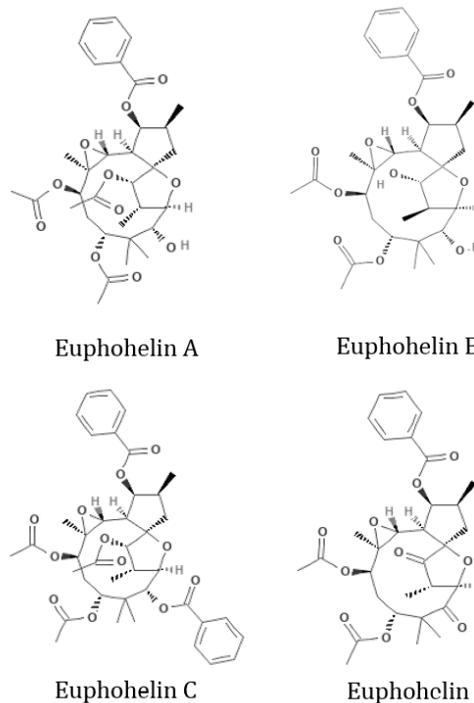


Euphohelin A
C₃₃H₄₄O₁₁

Euphohelin B
C₃₁H₄₂O₁₀

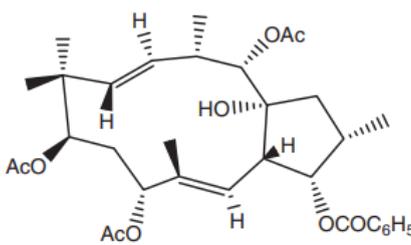
Euphohelin C
C₄₀H₄₈O₁₂

Euphohelin D
C₃₁H₃₈O₁₀



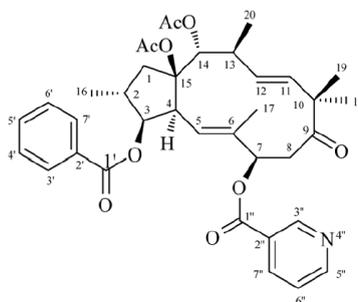
[61]

Euphornin
C₃₃H₄₄O₉

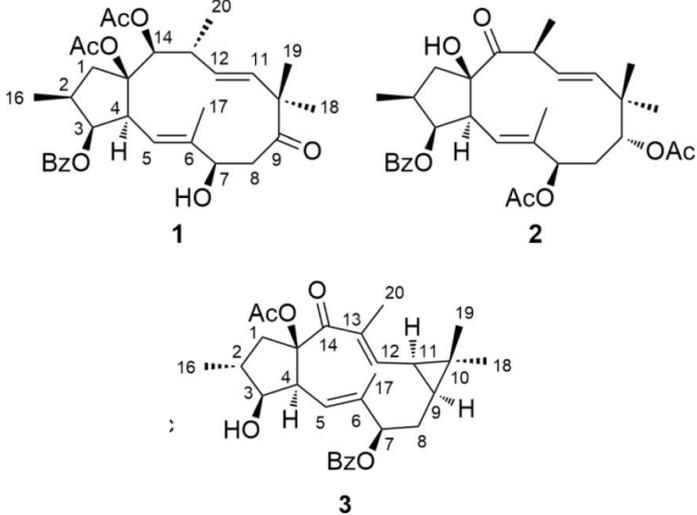
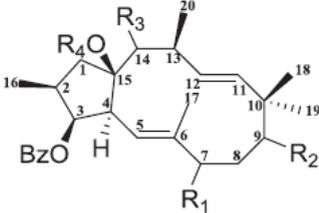
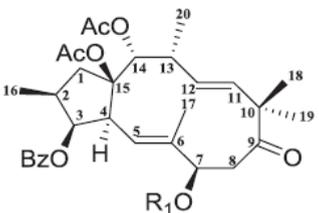
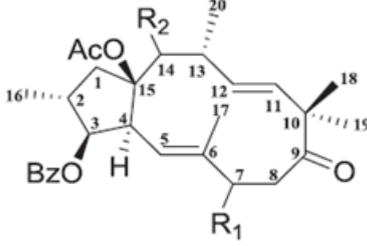


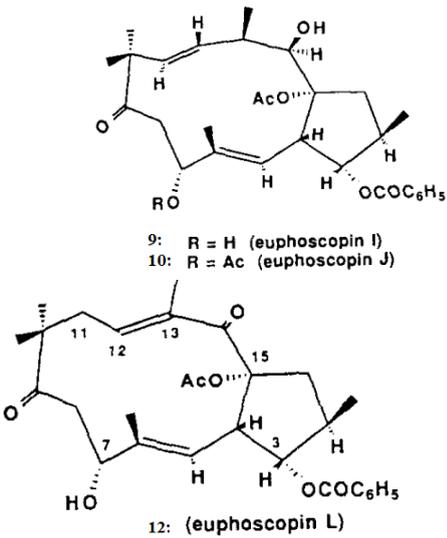
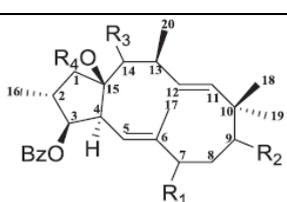
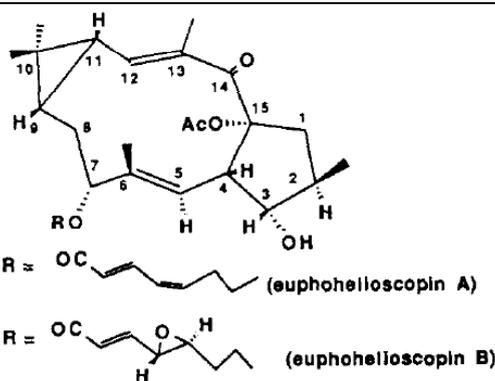
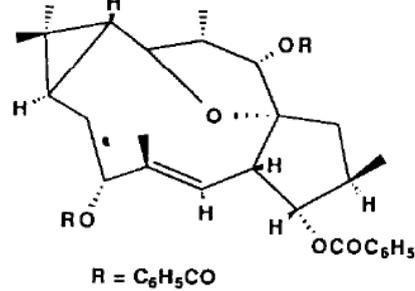
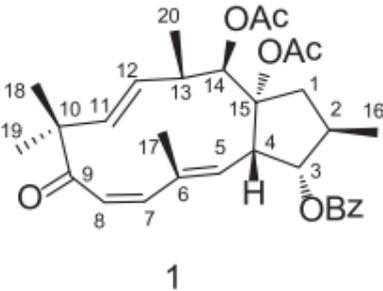
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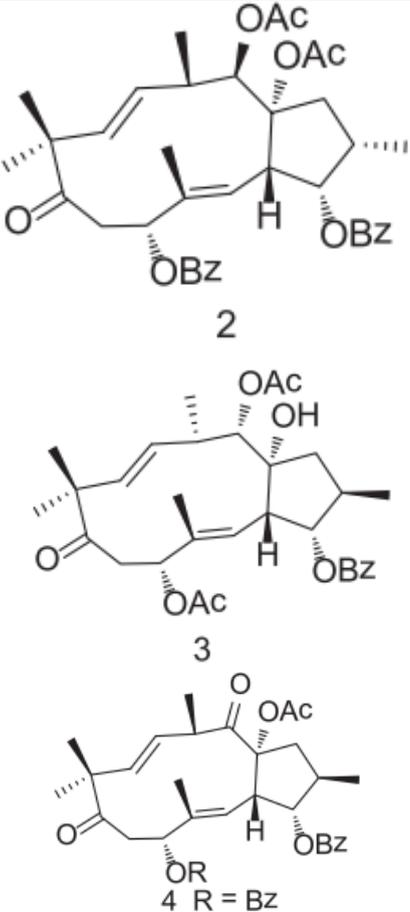
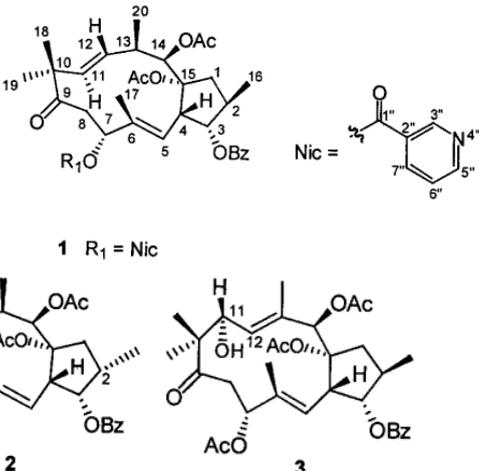
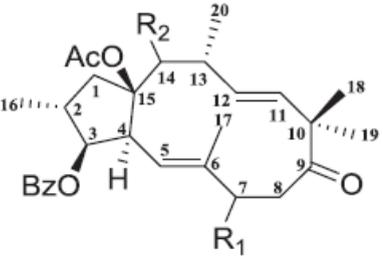
Euphoheliosnoid E
C₃₇H₄₃NO₉

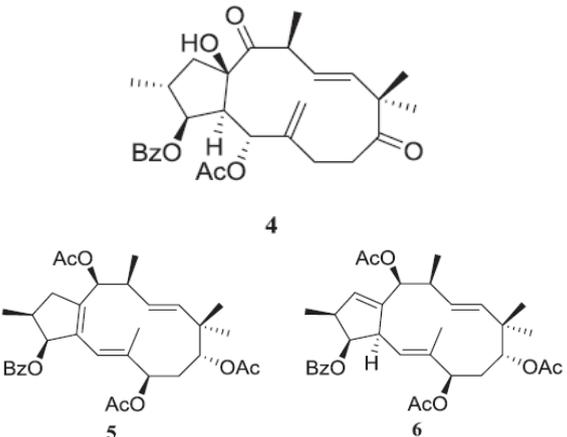
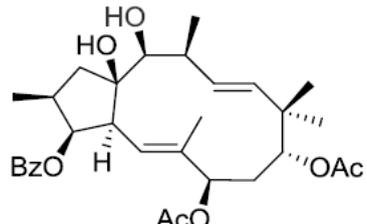
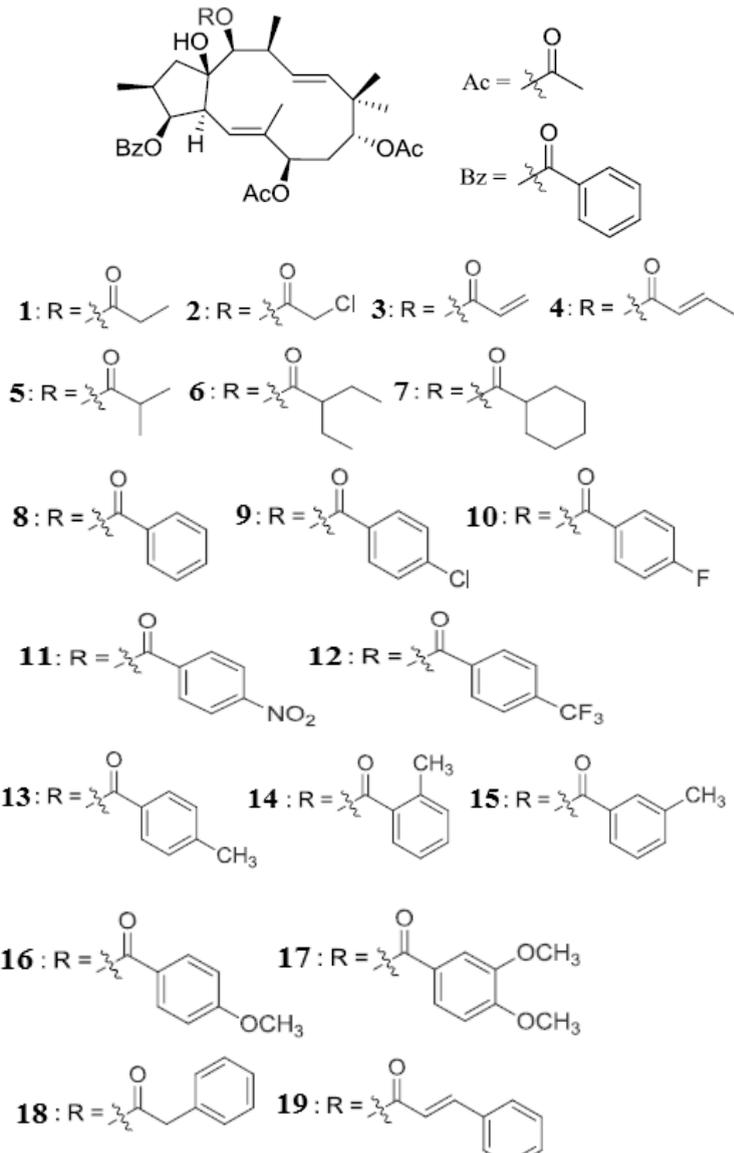
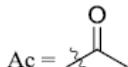
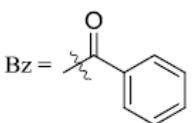
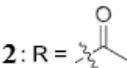
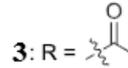
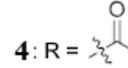
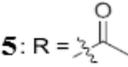
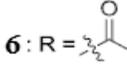
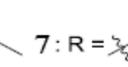
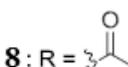
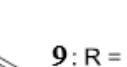
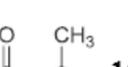
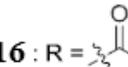
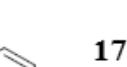
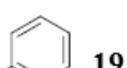


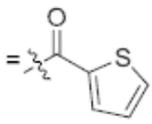
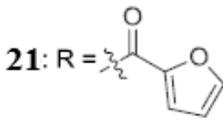
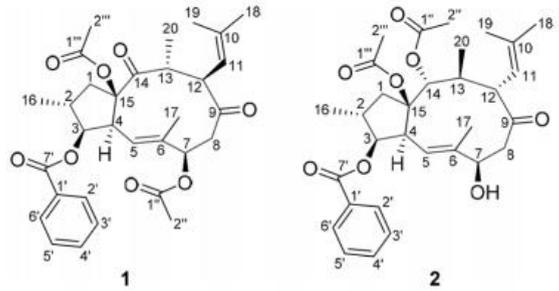
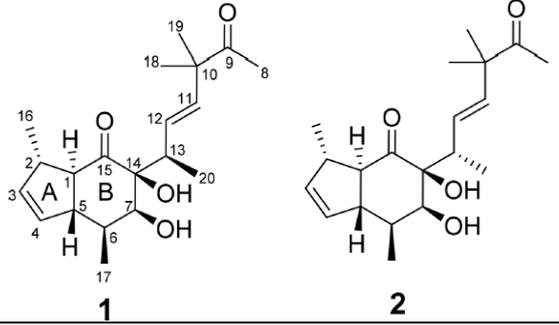
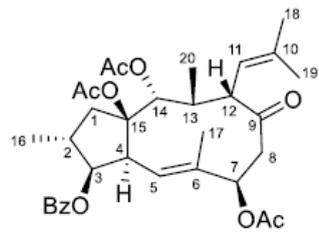
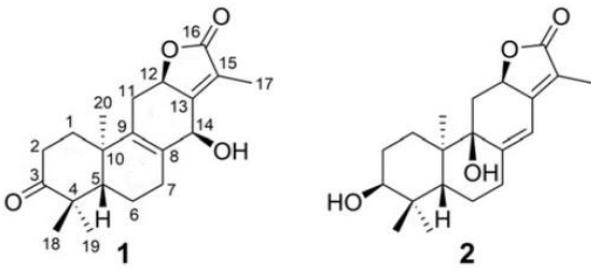
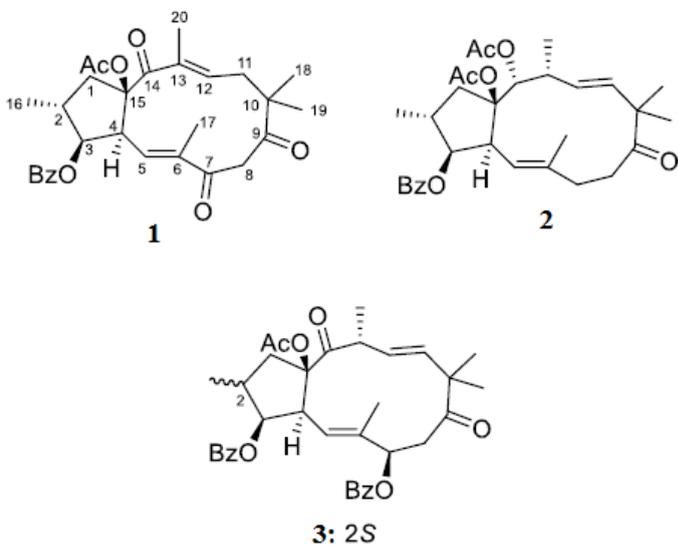
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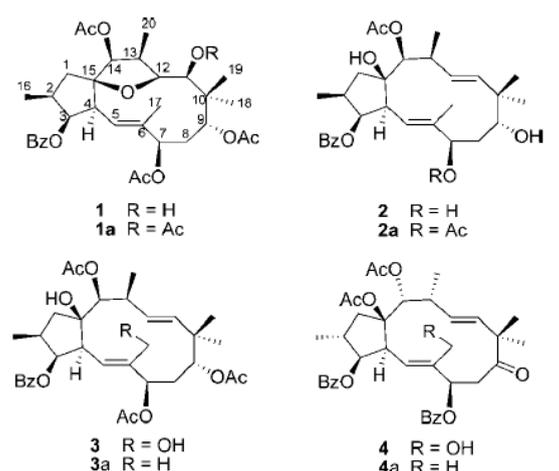
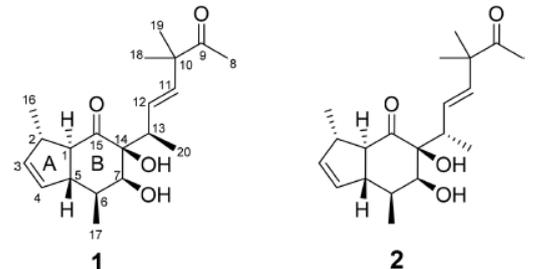
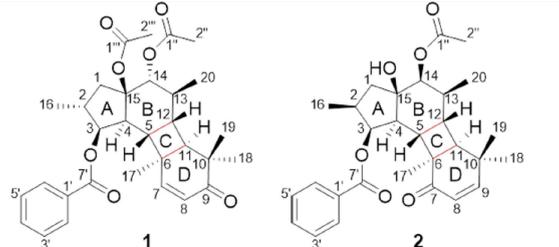
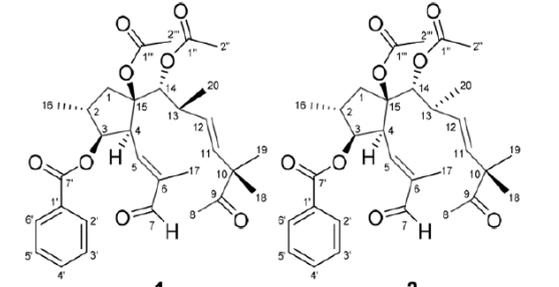
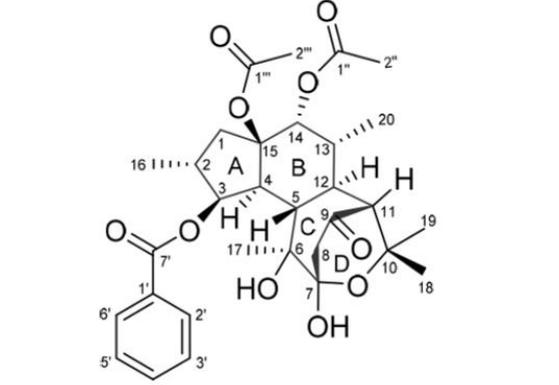
<p>Euphoscopoids A-C (1-3) 1: C₃₁H₄₀O₈ 2: C₃₁H₄₀O₈ 3: C₂₉H₃₆O₆</p>		[53]
<p>Euphornin A-K (1-11) 1: C₃₁H₄₁O₇ 2: C₃₁H₄₂O₇ 3: C₃₁H₄₀O₈ 4: C₃₅H₄₆O₁₀ 5: C₃₅H₄₆O₁₀ 6: C₂₉H₃₈O₇ 7: C₃₁H₄₀O₈ 8: C₃₃H₄₂O₉ 9: C₃₃H₄₂O₉ 10: C₃₁H₄₀O₈ 11: C₃₁H₄₀O₈</p>	 <p>1: R₁ = β-OH R₂ = α-OAc R₃ = β-OAc R₄ = H 3: R₁ = O R₂ = α-OAc R₃ = β-OAc R₄ = H 4: R₁ = β-OAc R₂ = α-OAc R₃ = α-OAc R₄ = Ac 7: R₁ = β-OAc R₂ = O R₃ = β-OAc R₄ = H 8: R₁ = β-OAc R₂ = O R₃ = α-OAc R₄ = Ac 9: R₁ = β-OH R₂ = O R₃ = α-OAc R₄ = Ac</p>  <p>10: R₁ = Ac 11: R₁ = H</p>	[54-62, 78]
<p>Euphoscopin A-L (1-12) 1: C₃₁H₄₀O₈ 2: C₃₃H₄₂O₉ 3: C₃₈H₄₄O₉ 4: C₃₁H₃₈O₈ 5: C₂₉H₃₆O₇ 6: C₃₁H₃₈O₈ 7: C₂₉H₃₈O₇ 8: C₃₁H₄₀O₈ 9: C₂₉H₃₈O₇ 10: C₃₁H₄₀O₈ 11: C₂₉H₃₉O₇ 12: C₂₉H₃₆O₇</p>	 <p>1: R₁ = β-OH R₂ = α-OAc 2: R₁ = β-OAc R₂ = α-OAc 3: R₁ = β-OBz R₂ = α-OAc 4: R₁ = O R₂ = α-OAc 5: R₁ = β-OH R₂ = O 6: R₁ = β-OAc R₂ = O 7: R₁ = H R₂ = AC 8: R₁ = R₂ = AC 11: R₁ = AC R₂ = H</p>	[54,62]

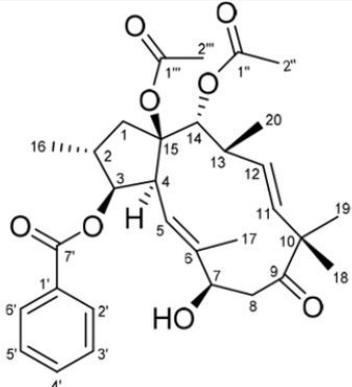
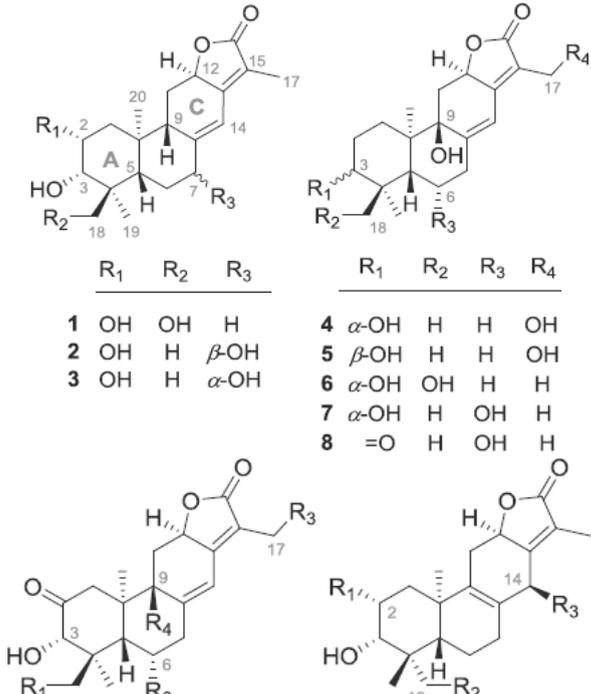
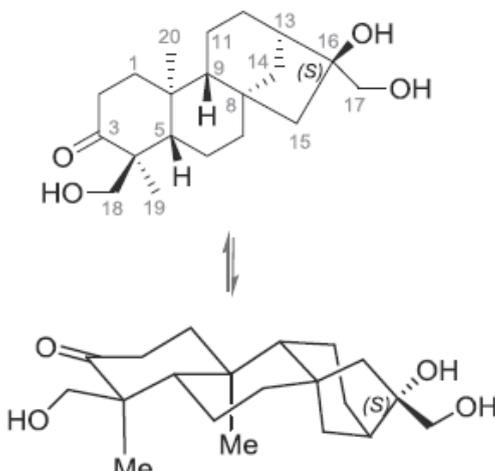
	 <p>9: R = H (euphoscopin I) 10: R = Ac (euphoscopin J)</p> <p>12: (euphoscopin L)</p>	
<p>Epieuphoscopin A-B (1-2) 1: C₃₁H₄₀O₈ 2: C₃₃H₄₂O₉ Epieuphoscopin D (3) 3: C₃₁H₃₈O₈ Epieuphoscopin F (4) 4: C₃₁H₃₈O₈</p>	 <p>1: R₁ = β-OH R₂ = O R₃ = α-OAc R₄ = Ac 2: R₁ = β-OAc R₂ = O R₃ = α-OAc R₄ = Ac 3: R₁ = O R₂ = O R₃ = α-OAc R₄ = Ac 4: R₁ = β-OAc R₂ = O R₃ = O R₄ = Ac</p>	[54,62]
<p>Euphohelioscopin A-B (1-2) 1: C₃₀H₄₂O₆ 2: C₃₀H₄₂O₇</p>	 <p>1: R = OC(CH₂)₁₀CH₃ (euphohelioscopin A) 2: R = OC(CH₂)₄CH(OH)CH₂CH₃ (euphohelioscopin B)</p>	[54]
<p>Euphohelionon C₁₄H₄₄O₇</p>	 <p>R = C₆H₅CO</p>	[54]
<p>Euphorbiapene A-D (1-4) 1: C₃₁H₃₈O₇ 2: C₃₈H₄₈O₉N 3: C₃₁H₄₁O₈ 4: C₃₆H₄₀O₈Na</p>	 <p>1</p>	[63, 62]

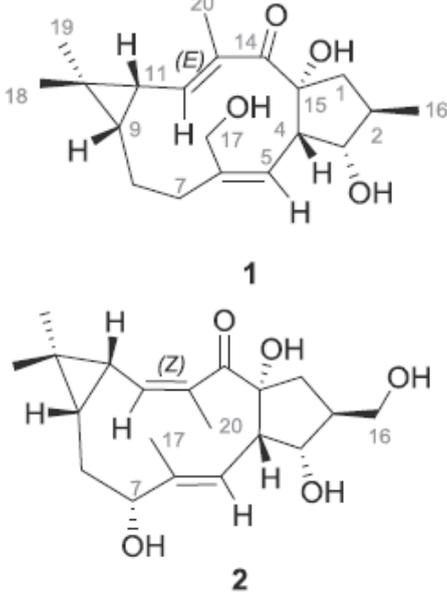
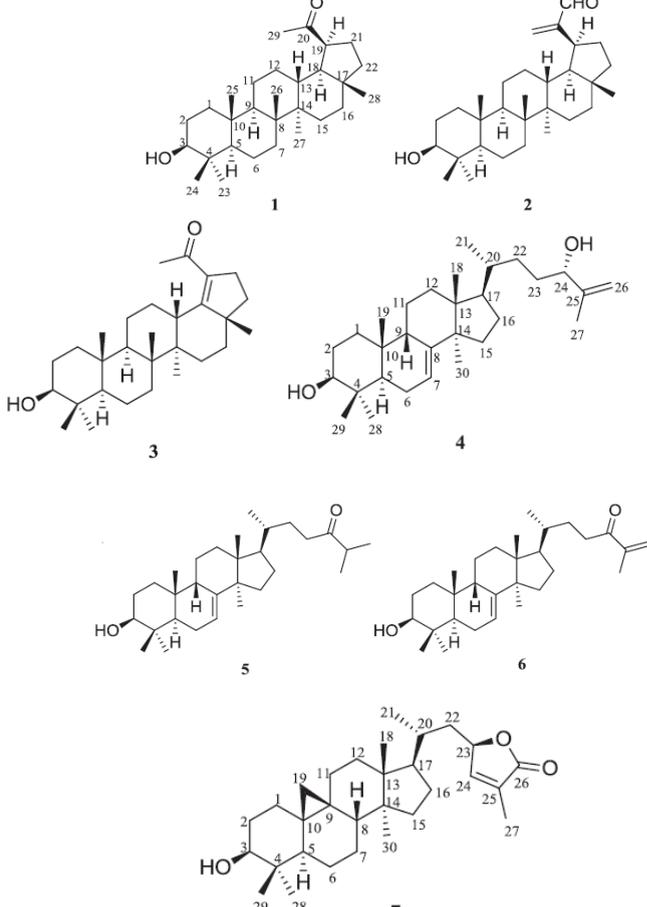
		 <p style="text-align: center;">2</p> <p style="text-align: center;">3</p> <p style="text-align: center;">4 R = Bz</p>	
	<p>Euphoheliosnoid A-C (1-3)</p> <p>1: C37H43NO9 2: C37H43NO9 3: C33H42O10</p>	 <p style="text-align: center;">1 R₁ = Nic</p> <p style="text-align: center;">2</p> <p style="text-align: center;">3</p>	[79]
	<p>Euphorpin A-F (1-6)</p> <p>1: C36H48O9Na 2: C35H46O9Na 3: C38H44O10Na 4: C29H36O7Na 5-6: C33H42O8Na</p>	 <p style="text-align: center;">1 R₁ = β-OMeBu R₂ = α-OAc 2 R₁ = β-OBu R₂ = α-OAc 3 R₁ = β-OSal R₂ = α-OAc</p>	[62]

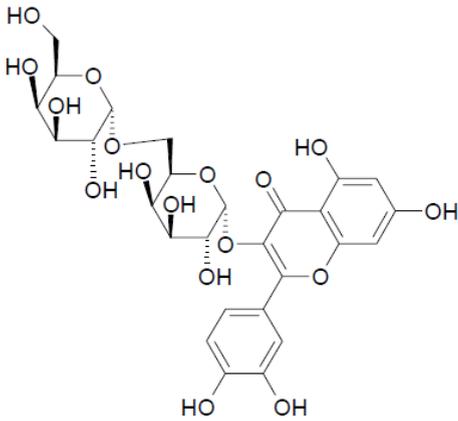
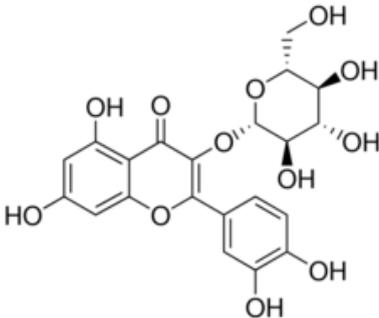
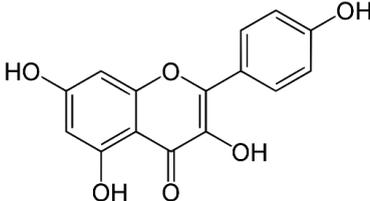
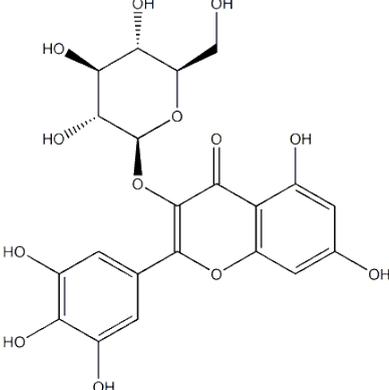
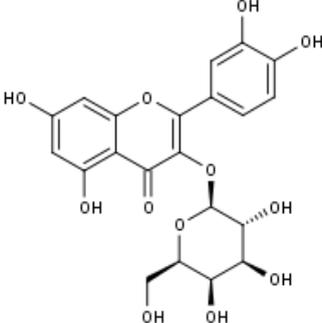
		 <p style="text-align: center;">4</p> <p style="text-align: center;">5 6</p>	
	<p>Monodeacetyleuphorin (C₃₁H₄₂O₈Na)</p>		[78]
	<p>Euphornoate A-U (1-21) 1: C₃₄H₄₆O₉Na 2: C₃₃H₄₃ClO₉Na 3: C₃₄H₄₄O₉Na 4: C₃₅H₄₆O₉Na 5: C₃₅H₄₈O₉Na 6: C₃₇H₅₂O₉Na 7: C₃₈H₅₂O₉Na 8: C₃₈H₄₆O₉Na 9: C₃₈H₄₅ClO₉Na 10: C₃₈H₄₅FO₉Na 11: C₃₈H₄₅NO₁₁Na 12: C₃₉H₄₅F₃O₉Na 13: C₃₉H₄₈O₉Na 14: C₃₉H₄₈O₉Na 15: C₃₉H₄₈O₉Na 16: C₃₉H₄₈O₁₀Na 17: C₄₀H₅₀O₁₁Na 18: C₃₉H₄₈O₉Na 19: C₄₀H₄₈O₉Na 20: C₃₆H₄₄O₉SNa 21: C₃₆H₄₄O₁₀Na</p>	 <p style="text-align: center;">RO</p> <p style="text-align: center;">HO</p> <p style="text-align: center;">BzO</p> <p style="text-align: center;">H</p> <p style="text-align: center;">AcO</p> <p style="text-align: center;">Ac = </p> <p style="text-align: center;">Bz = </p> <p>1: R =  2: R =  3: R =  4: R = </p> <p>5: R =  6: R =  7: R = </p> <p>8: R =  9: R =  10: R = </p> <p>11: R =  12: R = </p> <p>13: R =  14: R =  15: R = </p> <p>16: R =  17: R = </p> <p>18: R =  19: R = </p>	[78]

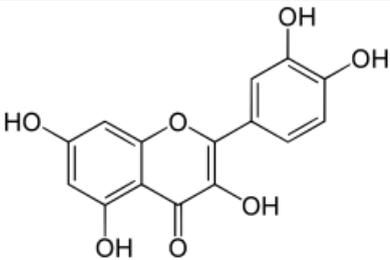
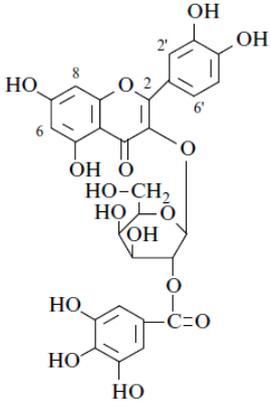
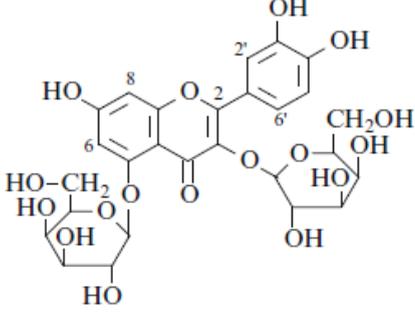
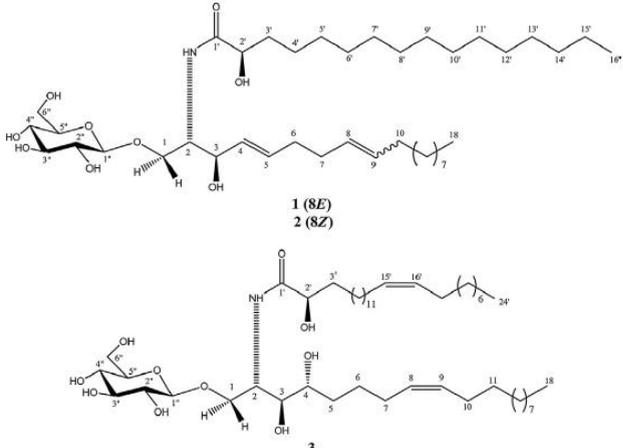
		<p>20: R = </p> <p>21: R = </p>	
<p>Heliojatrone A-B (1-2) 1: C₃₁H₃₈O₈ 2: C₃₁H₄₀O₈</p>		[80]	
<p>Euphorhelipane A-B (1-2) 1: C₂₀H₃₀O₄ 2: C₂₀H₃₀O₄</p>		[81]	
<p>Heliojatrone C C₃₃H₄₂O₉Na</p>		[82]	
<p>Euphcopenoid A-B (1-2) 1: C₂₀H₂₆O₄ 2: C₂₀H₂₈O₄</p>		[83]	
<p>Euphoscopoid D-F (1-3) 1: C₂₉H₃₄O₇Na 2: C₃₁H₄₀O₇Na 3: C₃₆H₄₀O₈N</p>		[82]	

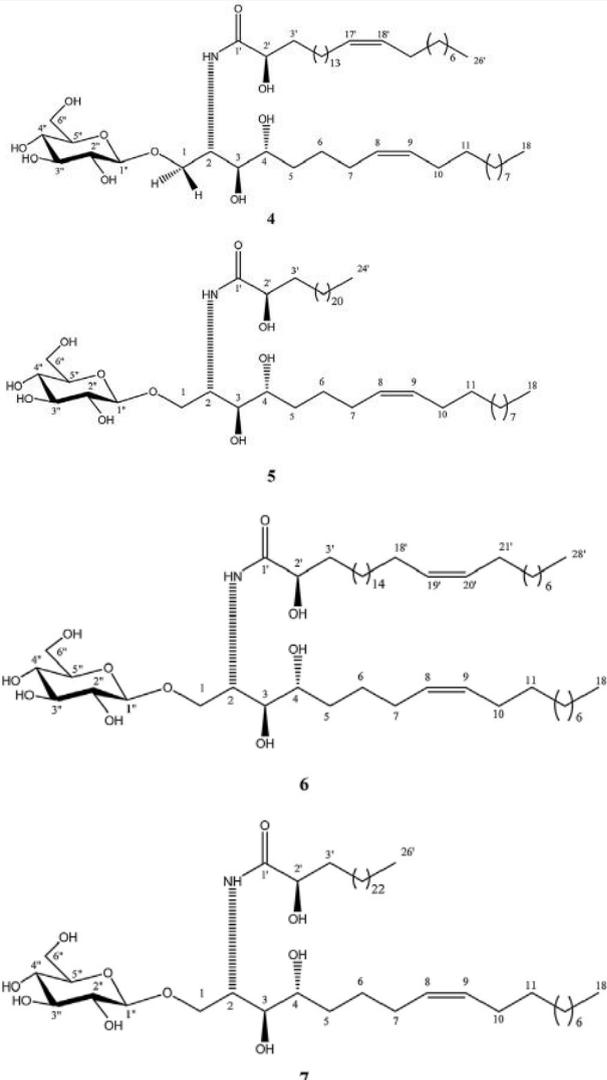
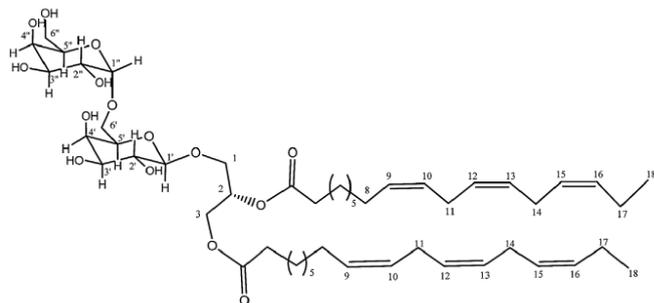
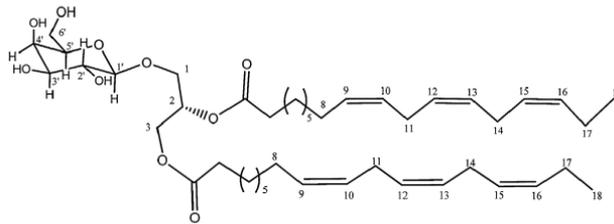
<p>Jatrophone-type diterpenoids (1-4)</p> <p>1: C33H44O10 2: C29H40O7 3: C33H44O10 4: C38H44O10</p>	 <p>1 R = H 1a R = Ac</p> <p>2 R = H 2a R = Ac</p> <p>3 R = OH 3a R = H</p> <p>4 R = OH 4a R = H</p>	[11]
<p>Euphorhelipanes A-B (1-2)</p> <p>1: C20H30O4 2: C20H30O4</p>	 <p>1</p> <p>2</p>	[8]
<p>Heliosterpenoids A-B (1-2)</p> <p>1: C31H38O7Na 2: C29H36O6Na</p>	 <p>1</p> <p>2</p>	[84]
<p>Secoheliosphanes A and B (1-2)</p> <p>1: C31H40O8 2: C31H40O8</p>	 <p>1</p> <p>2</p>	[85]
<p>Secoheliospholane A C31H40O10</p>		[85]

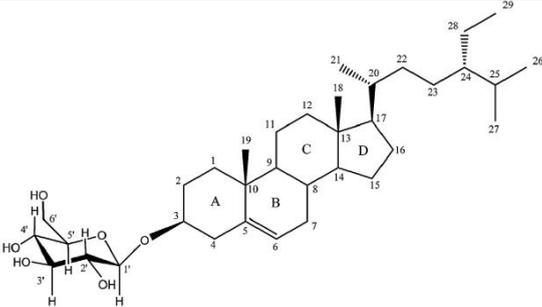
<p>2-epi-Euphornin I C₃₁H₄₀O₈</p>		[85]																																																																																						
<p>Euphelinolide A-N (1-14) 1-7: C₂₀H₂₈O₅Na 8-9: C₂₀H₂₆O₅Na 10-11: C₂₀H₂₆O₆Na 12-13: C₂₀H₂₈O₅Na 14: C₂₀H₂₆O₅Na</p>	 <table border="1" data-bbox="654 806 1165 1411"> <thead> <tr> <th colspan="3">R₁ R₂ R₃</th> <th colspan="4">R₁ R₂ R₃ R₄</th> </tr> </thead> <tbody> <tr> <td>1</td><td>OH</td><td>OH</td><td>H</td> <td>4</td><td>α-OH</td><td>H</td><td>H</td><td>OH</td> </tr> <tr> <td>2</td><td>OH</td><td>H</td><td>β-OH</td> <td>5</td><td>β-OH</td><td>H</td><td>H</td><td>OH</td> </tr> <tr> <td>3</td><td>OH</td><td>H</td><td>α-OH</td> <td>6</td><td>α-OH</td><td>OH</td><td>H</td><td>H</td> </tr> <tr> <td></td><td></td><td></td><td></td> <td>7</td><td>α-OH</td><td>H</td><td>OH</td><td>H</td> </tr> <tr> <td></td><td></td><td></td><td></td> <td>8</td><td>=O</td><td>H</td><td>OH</td><td>H</td> </tr> <tr> <th colspan="4">R₁ R₂ R₃ R₄</th> <th colspan="3">R₁ R₂ R₃</th> </tr> <tr> <td>9</td><td>OH</td><td>H</td><td>H</td><td>H</td> <td>12</td><td>OH</td><td>H</td><td>OH</td> </tr> <tr> <td>10</td><td>H</td><td>OH</td><td>H</td><td>OH</td> <td>13</td><td>H</td><td>OH</td><td>OH</td> </tr> <tr> <td>11</td><td>H</td><td>H</td><td>OH</td><td>OH</td> <td>14</td><td>H</td><td>OH</td><td>=O</td> </tr> </tbody> </table>	R ₁ R ₂ R ₃			R ₁ R ₂ R ₃ R ₄				1	OH	OH	H	4	α -OH	H	H	OH	2	OH	H	β -OH	5	β -OH	H	H	OH	3	OH	H	α -OH	6	α -OH	OH	H	H					7	α -OH	H	OH	H					8	=O	H	OH	H	R ₁ R ₂ R ₃ R ₄				R ₁ R ₂ R ₃			9	OH	H	H	H	12	OH	H	OH	10	H	OH	H	OH	13	H	OH	OH	11	H	H	OH	OH	14	H	OH	=O	[86]
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<p>6-Epi-18-hydroxy-abbeokutone C₂₀H₃₂O₄Na</p>		[86]																																																																																						

	<p>Eupheliotriol A-B (1-2) 1: C₂₀H₃₀O₄Na 2: C₂₀H₃₀O₅Na</p>	 <p style="text-align: center;">1</p> <p style="text-align: center;">2</p>	[86]
Triterpenes	<p>Euphorbatrine A-G (1-7) (19αH)-lupane : (1-2) : 1 : C₂₉H₄₈O₂ 2 : C₃₀H₄₈O₂ 3 : C₂₉H₄₆O₂ (9βH)-lanostane : (4-6) 4 : C₃₀H₅₀O₂ 5 : C₃₀H₅₀O₂ 6 : C₃₀H₄₈O₂ 7 : C₃₀H₄₆O₃</p>	 <p style="text-align: center;">1</p> <p style="text-align: center;">2</p> <p style="text-align: center;">3</p> <p style="text-align: center;">4</p> <p style="text-align: center;">5</p> <p style="text-align: center;">6</p> <p style="text-align: center;">7</p>	[68]

Flavonoids	Heliosin $C_{27}H_{30}O_{17}$		[56, 71]
Falavones	Quercetin-3-O-glucoside $C_{21}H_{19}O_{12}$		[87]
Flavonols	Kaempferol $C_{15}H_{10}O_6$		[88]
Flavonol glycosides	Isomyricitrin $C_{21}H_{20}O_{13}$		[75]
Glucosides	Hyperoside $C_{21}H_{20}O_{12}$		[56, 75]

	<p>Quercetin C₁₅H₁₀O₇</p>		[56, 75]
	<p>Quercetin-3-O-β, galactoside-2"-galate C₂₈H₂₄O₁₆</p>		[87]
	<p>Titimalin (Quercetin- 5,3-digalactoside) C₂₇H₃₀O₁₇</p>		[70-89, 90]
Glycosphingolipides	<p>Cerebrosides 1-7 C₄₁H₇₇NO₉</p>	 <p>1 (8E) 2 (8Z) 3</p>	[59]

		 <p>4</p> <p>5</p> <p>6</p> <p>7</p>	
<p>Galactolipids</p>	<p>Digalactosyldiacylglycerol</p>		<p>[59]</p>
	<p>Monogalactosyldiacylglycerol</p> <p>$C_{43}H_{76}O_{10}$</p>		<p>[59]</p>

Lipids	Glucoclionasterol $C_{35}H_{60}O_6$		[59]
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Pharmacological properties

In literature, twenty five pharmacological activities (table 2) were reported in relation with *E. helioscopia* L. References of studies describing these activities are summarized in table 3 below and are chronologically classified as described in the literature.

Table 2: Different biological activities of *Euphorbia helioscopia*

Pharmacological activity	References
Antibacterial activity	[1-5-7-77-91,93]
Antiviral activity	[7,85]
Antioxidant activity	[1-13-14,15]
Antifungal activity	[1-16,95]
Phytotoxic activity	[1]
Anthelmintic activity	[8, 96]
Antitumor activity	[9,68]
Anti-allergic activity	[76]
Anti-asthmatic activity	[76]
Cytotoxic activity	[(10-11-53,84]
Anticancer activity	[12-41-92-91,94]
Allelopathic activity	[98,99]
Anti-nociceptive activity	[15]
Anti-inflammatory activity	[15,82]
Anti-pyretic activity	[15]
Vasodepressor activity	[3]
Free-radical scavenging activity	[59]
Antifeedant	[53]
Inhibitory activity	[63]
Antileishmanial Activity	[100]
Catalytic activity	[101]
P-glycoprotein (P-gp) inhibitory	[84]
Lipid-lowering activity	[62]
Multidrug resistance modulators activity	[78]
Triglyceride-lowering activity	[8]

The most interesting active compounds from *E. helioscopia* L. belongs to diterpenoids [9, 12]. For example, the bioactive jatropane diterpenoids, heliosterpenoids A & B were found to be potent inhibitors of P-glycoprotein (ABC1) and exhibited cytotoxicity against MDA-MB-231 cell lines [85]. The same Helioscopianoids A–Q showed neuroprotective activities against serum deprivation-induced PC12 cell damage [80], eupheliolides F and L diterpenoids exhibited significant cytotoxicity against MCF-7 and PANC-1 cell lines [86]. Triterpenoids Euphorbatrine E and F increased Hela–/– cell death via activating apoptosis pathway other than necroptosis [68]. And the most relevant activities are antibacterial [1-5-7-66-91, 93], antioxidant [1-13-14, 15] and anticancer [12-41-92-91, 94]. As previously described, *E. helioscopia* L. has several properties, among them its

antioxidant activity *E. helioscopia L.* flowers extracts have the highest levels of phenolics and flavonoids, as well as highest antioxidant compared to leaf and stem extracts, regardless of the solvent used [14]. Another study reported that methanolic extracts of *E. helioscopia L.* leaves possess significant antioxidant activity in vivo by increasing biomarkers of oxidative stress in tissue and homogenates serum enzymes [15].

Among bioactive functions of *E. helioscopia L.*, some studies mentioned an antiviral and antibacterial effect [6-7, 8]. In addition, it has been reported that antibacterial activity of dichloromethane and methanol extracts from aerial parts of *E. helioscopia L.* was performed against *Escherichia Coli*, *Bacillus Subtilis*, *Shigella Flexenari*, *Staphylococcus Aureu*, *Pseudomonas Aeruginosa* and *Salmonella Typhi* [1]. *E. helioscopia L.* was active against *Bacillus Anthracis* [5]. As well as extracts from *E. helioscopia L.* had an inhibition of more than 90% against *Botrytis Cinerea*, *Rhizoctonia*, *Solani*, *Fusarium Oxysporum*, *Cladosporium Cucumerinum* and *Alternaria Solani Fungi* [16].

Isolated compounds (*Euphornin L.* and *Euphoscopin*) of *E. helioscopia L.* exhibited cytotoxicity against HL-60 [10]. Extracts of *E. helioscopia L.* from Turkey showed a vasodepressor effect which could be due to its vasorelaxant activity [3]. *E. helioscopia L.* also showed an anticancer effect; indeed, ethyl acetate and chloroform extracts could inhibit the proliferation of five human cancer cell lines over a range of concentrations from 50 to 200 µg / mL [12]. Park's study [76] indicates that polyphenol compound known as helioscopinin-A has shown some inhibitory activity of capillary permeability in responses to passive cutaneous anaphylaxis in rats. The whole plant of *E. helioscopia L.* has significant anthelmintic activity, which may be a potential alternative to treating helminth infections in ruminants [96]. Studies showed that *E. helioscopia L.* have innumerable benefits especially from aerial parts, such as antioxidant, antiviral, antitumoral, antibacterial, antifungal, anti-allergic, anti-asthmatic allelopathic, lipid and triglyceride lowering activity and other effects, it is very promising as anthelmintic.

Table 3 below provides a summary of reported pharmacological activities, details of extracts, application type (in vivo or in vitro), test objective, used control; doses tested for drugs and found results. Among the thirty nine studies about pharmacological activities, 40 % of presented tests were conducted in vivo, 10% of them are performed in vivo and in vitro. Where extracts from all parts of the plant were used to determine these pharmacological proprieties. Encouraging findings can be considered as a scientific demonstration of the different historical uses of this plant as drug as specified in the chapter 3 of this review.

All previously cited researchers used the whole plant of *E. helioscopia L.* for their studies. However, there are no studies that use each organ (roots, stems, leaves or flowers) of the plant separately and compare their effects for example. The same remark is applicable for comparison of different methods of extraction or solvents that give the best yield extracts. Studies show that *E. helioscopia L.* countless health benefits, such as antibacterial, antiviral, antioxidant, antifungal, anthelmintic, antitumor, anti-allergic, anti-asthmatic, cytotoxic, anticancer. Also, it is very promising as lipid- and Triglyceride-lowering activities. Thus, the pharmacological activities should be fully explored with in-depth in vitro and in vivo tests, and, ultimately, clinical trials to prove these activities in humans (Table 3).

Table 3: Main pharmacological activities of *Euphorbia helioscopia*

Pharmacologic al activity	Extract details	In vivo / in vitro test	Objective	Used control	Dose tested for drugs	Findings	Reference s
Antibacterial activity	Methanol extracts of <i>E. helioscopia L.</i>	In vitro	To evaluate the antibacterial activity of 306 plants from 52 families from northeastern Iran (Khorasan province), including <i>E. helioscopia L.</i>	In each plate, a positive control (gentamycin 0.8 mg / 0.2 ml or clotrimazole 8 µg / 0.2 ml) and negative control (methanol 0.2 ml) were included.	Crude extracts (0.2 ml), corresponding to 0.5 g of powdered plant / ml of extract.	Methanol extracts from <i>E. helioscopia L.</i> reported a significant effect against <i>Bacillus Anthracis</i> .	[5]
Antitumor Activity	Aquatic extract of <i>E. helioscopia L.</i> roots	In vitro	3 types of cancer cells were used to assess the antitumor activity.	Control cells exhibited normal morphology.	1.43, 1.67, 0.97mg/ml of aquatic extract.	<i>E. helioscopia</i> extracts (4mg/ml) inhibited 7721, Hela, MKN-45 cells with 59.8%, 66.4%, 70.5%. They had obvious antitumor activity.	[9]
Anti-Allergic and Anti-Asthmatic activities	Extraction of polyphenol compound, helioscopinin-A.	In vivo: rats and pigs	To identify the chemical nature of principal active	Control of relaxant activity: positive reference FPL 55712 (100 µg/ml). Control of allergic response : Rat passive cutaneous anaphylaxis (45mg/kg of Helioscopinin-A)	Relaxant activity: 500, 1000 µg/ml of extract of <i>E. helioscopia L.</i> . Allergic response: - 1mg/ml of Helioscopinin-A for rat mast cell Histamine release test - 30 mg/ml of Helioscopinin-A	Helioscopinin-A showed an anti-allergic and anti-asthmatic activity.	[76]

					for asthmatic bronchial constriction - 0.1; 0.5; 1 mg/ml of Helioscopinin-A for leukotriene D4 introduced tracheal contraction - 0.1 et 1 mg/ml of Helioscopinin-A for leukotriene D4 induced ileal contraction.		
Antimicrobial activity	0.25 g leaf of each species was ground in a braying mortar, then 2.5 ml or 5 ml DMSO or ethanol was added in order to prepare solutions	In vitro	To study <i>E. helioscopia</i> L. activity against <i>Bacillus subtilis</i> , <i>Staphylococcus aureus</i> , <i>Escherichia coli</i> and <i>Candida albicans</i> .	Control discs were soaked in ethanol and DMSO.	0.05 g/ml and 0.1 g/ml	<i>E. helioscopia</i> L. proved to be the most effective against <i>Bacillus subtilis</i> , <i>Staphylococcus aureus</i> , <i>Escherichia coli</i> and <i>Candida albicans</i> .	[6]
Antifungal activity	Extracts of 14 plants including: <i>E. helioscopia</i> L..	In vitro	To evaluate antifungal activity of 14 plants' extracts against fungi: <i>Botrytis Cinerea</i> , <i>Rhizoctonia Solani</i> , <i>Fusarium Oxysporum</i> , <i>Cladosporium Cucumerinum</i> et <i>Alternaria Solani</i>	Control: without treatment.	Concentration of extracts was 0.1 g / ml. Using methods of growth rate and spore germination.	Extracts of <i>X. sibiricum</i> , <i>E. helioscopia</i> L., <i>S. flavescens</i> , <i>S. nigrum</i> , <i>A. Annuum</i> and <i>T. mongolicum</i> had an inhibition rate superior than 90% in spore germination of at least one tested fungus.	[16]
Cytotoxic activity	Euphornin L, and seven known analogues were isolated from <i>E. helioscopia</i> L..	In vitro	To extraire Euphornin L, and seven analogues and evaluate their toxicity against HL-60.	Control: without treatment.	2.7 and 9.0 μM .	Euphornin L and euphoscopin F showed significant cytotoxicity to HL-60 cell lines with LC_{50} values of 2.7 and 9.0 μM .	[10]
Antiviral and Antibacterial activities	Soxhlet and maceration in methanol extracts of aerial parts of <i>E. helioscopia</i> L.	In vitro	To evaluate antiviral activity using plaque reduction assay	Negative control: contained all content for treatment except for replacement of bacterial suspension with PA Top Agar medium. Positive control: plate the extract was replaced with 500 μL trifluridine.	Sterile Eppendorf micro-centrifuge tubes (polypropylene; 1.5 mL; Sarstedt) were used. Each tube contained colony-forming units (cfu ml^{-1}) of <i>Bacillus Cereus</i> ATCC 10876 cultures, serially diluted <i>E. helioscopia</i> L. extract in distilled water (62.5, 125, 250, 375, 500, 750, 1000 and 1250 $\mu\text{g.mL}^{-1}$) and respective growth	Macerated extract showed the high reduction of the number of plaques in other hand extracts by Soxhlet method might destroy the active compounds.	[7]

					medium .		
Cytotoxic activity	Four jatrophane-type diterpenoids, were isolated from <i>E. helioscopia L.</i>	In vitro	To evaluate isolated compounds effect against HeLa and MDA-MB-231 cells.	Adriamycin as a positive control (LC50) 0.41 μ M against HeLa cells and 0.34 μ M against MDA-MB-231 cells).	-	Helioscopinolid e A and Euphornin showed cytotoxic activity	[11]
Antioxidant, antifungal, antibacterial and phytotoxic activities	Dichloromethane and methanol extracts from the aerial parts of <i>E. helioscopia L.</i>	In vitro	To evaluate antioxidant, antifungal, antibacterial and phytotoxic activities of <i>Euphorbia Helioscopia</i> extracts.	Control: Without treatment.	-	Dichloromethane extract showed significant activity against <i>Fusarium Solani</i> with 90% inhibition, where the same extract also showed non-significant activity against <i>Salmonella Typhi</i> and <i>Bacillus Subtilis</i> . The methanolic extract has a promising radical scavenger activity in this assay. Both extracts have non-significant phytotoxicity on <i>Lemna Minor</i> .	[1]
Multidrug resistance activity in cancer therapy	EtOAc extract of <i>E. helioscopia L.</i> offered Jatrophane and lathyrene diterpenes.	In vitro	To investigate of the aerial parts of <i>Euphorbia</i> spices among them <i>E. helioscopia L.</i> , to isolate their bioactive metabolites and to test their multidrug resistance activity.	Cyclosporin A (CsA) was used as a reference inhibitor.	Compounds were tested at concentrations of 0, 0.5, 2.0, 2.5, 10, 20 μ M	<i>E. helioscopia L.</i> , appeared to be specific inhibitors of Pgp since they showed no significant activity against BCRP, thus resembling to the third-generation class of specific MDR inhibitors.	[41]
Allelopathic activity	Aqueous extracts of root, stem, leaf, and fruit were prepared by soaking dried plant parts of <i>E. helioscopia L.</i> in water (1:20 w/v) for a period of 24 h.	In vivo: wheat, chickpea, and lentil.	To study the effects of extract from different parts of <i>E. helioscopia L.</i> on wheat, chickpea, and lentil germination and seedling growth, and to compare the allelopathic potential of various plant parts of <i>E. helioscopia L.</i>	Control: Distilled Water	In each petri dish 72 mL of extract or distilled water was added according to the treatment to avoid the drying out of seedlings throughout the growth period.	Water extracts from <i>E. helioscopia L.</i> 's root, stem, leaf and fruit resulted in a reduction in the seed germination (chickpea and lentil only) and germination index; but leaf extracts increased the mean germination time in all test crops.	[98]
Antioxidant	Methanol	In vitro	To evaluate	DPPH solution	Different	Extracts of	[13]

activity	extracts		antioxidant activity of total methanol extracts from 54 species of 30 families which <i>E. helioscopia L.</i> among them.	plus methanol was used as a control	concentrations of extracts (10, 20, 50, 100, 200 and 300 µg/mL, in methanol) were added at an equal volume (2.5 mL) to methanolic solution of DPPH (0.3 mM, 1 mL).	<i>E. helioscopia</i> was among plant exhibited the strongest activity.	
Anticancer activity	Extracts with aqueous ethanol; petroleum ether extract (PEE), ethyl acetate extract (EAE), chloroform extract (CE) and n-butanol extract (NBE) from <i>Euphorbia Helioscopia L.</i>	In vitro	To evaluate the growth inhibitory effects of <i>E. helioscopia L.</i> extracts on five different human cancer cells; Human hepatocellular carcinoma cell lines SMMC-7721, BEL-7402, HepG2, gastric carcinoma cell line SGC-7901 and colorectal cancer cell line SW480.	The control cells exhibited normal morphology of nucleolus, cytoplasm and organelles.	Latex and leaves methanol extract (600 and 1.200 mg/kg) orally, once a day, were given to mice for two weeks.	- Ethyl acetate extract and CE could inhibit the proliferation of all five human cancer cell lines at the concentration range of 50 to 200 µg/mL. - Flavonoids could be the main constituents of EAE.	[12]
Antioxidant activity	Methanolic and ethanolic extracts of <i>E. helioscopia L.</i> aerial parts.	In vitro	To evaluate total phenolics, flavonoids contents of methanolic and ethanolic extracts of <i>E. helioscopia L.</i> leaves, flowers and stem and examine their antioxidant proprieties using DPPH radical scavenging assay.	Positive control: Trolox (6-hydroxyl-2578 tetramethylchrom e-2-carboxylic acid)	1ml of each sample extract of varying concentrations (20, 50, 100, 200 and 500µg/ml) was mixed with 2ml of DPPH methanol solution (10-4M).	Extracts from <i>Euphorbia Helioscopia</i> , flowers had the highest phenolic and flavonoids content as well as the highest antioxidant potency compared to extracts from leaves and stem, regardless the solvent used.	[14]
Anthelmintic activity	Aqueous and methanol extracts of stem, leaves and flowers of <i>E. helioscopia L.</i>	In vitro: A worm motility inhibition (WMI) assay and egg hatch assay (EHA) In vivo: sheeps (faecal egg count reduction (FECR) assay was used)	To evaluate the in vitro and in vivo anthelmintic activity of <i>E. helioscopia L.</i>	Positive control: Levamisole (0.125 mg.ml ⁻¹) Negative control: 1 ml of phosphate buffer saline	Different concentrations (12.5 mg.ml ⁻¹ , 25 mg.ml ⁻¹ and 50 mg.ml ⁻¹) of aqueous and methanolic extracts were used against <i>H. Contortus</i> .	The entire plant of <i>E. helioscopia L.</i> possesses significant anthelmintic activity and could be a potential alternative for treating cases of helminth infections in ruminants.	[96]
Anthelmintic and antimicrobial activity	The powdered plant parts (500 g) were extracted with distilled water (2,000 ml) at 90–100 °C; then, same material was air dried at ambient room	In vitro: worm motility inhibition assay and egg hatch assay In vivo: Kashmir Marino sheep of	Evaluate the anthelmintic and antimicrobial efficacy of <i>Euphorbia Helioscopia</i> crude extracts.	Control: without treatment	Different concentrations (12.5 mg/ml, 25 mg/ml, 1 and 50 mg/ml) of aqueous and methanolic extracts were used against <i>H. Contortus</i> which exhibited dose-	<i>E. helioscopia L.</i> showed an effect against gastrointestinal nematodes and some selected veterinary pathogenic microbes suggest an alternative to	[97]

	temperature. Methanolic extraction (2,800 ml, Qualigens) was done at 60 °C in a Soxhlet extractor using a sequence of solvents for 8 h.	both sexes (1 year of age)			dependent anthelmintic effects on <i>H. Contortus</i> . The antimicrobial activity of extracts ranging from 100 to 500 mg.ml ⁻¹ screened by disc diffusion method against four selected bacteria (<i>Staphylococcus Aureus</i> , <i>Klebsiella Pneumoniae</i> , <i>Pseudomonas Multocida</i> and <i>Escherichia Coli</i>) and two fungal strains (<i>Aspergillus Flavus</i> and <i>Candida Albicans</i>)	the use of commercially available anthelmintics and antimicrobials for the treatment of sheep's gastrointestinal diseases.	
Inhibitory activity	Methanol extract of whole plants <i>E. helioscopia L.</i>	In vitro	To evaluate inhibitory activity on lipopolysaccharide (LPS)-induced NO production in murine microglial BV-2 cells	SMT (2-methyl-2-thiopseudourea, sulfate) was used as a positive control.	From 17 to 77 µM	All the evaluated diterpenes exhibited inhibitory effects on LPS-induced NO production	[63]
Antioxidant activity	Methanol extract of leaves and Latex from <i>E. helioscopia L.</i> steams.	In vivo: mice	To evaluate in vivo antioxidant activity of latex and leaves methanol extract of <i>E. helioscopia L.</i>	Control: without treatment.	Latex and leaves methanol extract (600 and 1 200 mg/kg) orally, once a day, were given to mice for two weeks.	Leaves methanol extract of <i>E. helioscopia L.</i> raised antioxidant enzymes levels in mice. It showed hepatorenal-curative effect, hypolipidemic effect and hemostasis potential.	[15]
Free-radical scavenging activity.	Methanolic leaves extracts of <i>E. helioscopia L.</i>	In vitro	The free-radical scavenging activity of the crude extract as well as of each isolated fraction was assayed and compared to that one of a commercial standardized antioxidant extract of green tea.	Tea extract (Green Select®)	Both samples and standard were dissolved in ethanol containing up to 2% DMSO at concentration of 6 mg/mL. Reaction mixture was prepared by adding 100 µl of extract solution (or standard solution) to 3.9 mL of DPPH solution, freshly prepared dissolving DPPH in methanol/KH2P	An interesting free-radical scavenging activity % was evidenced, since <i>E. helioscopia L.</i> reached a maximum effect (E _{max}) of 60% at 15 µg/mL and with an EC ₅₀ value of 6.9 µg/mL.	[59]

					O4 and NaOH buffer (50/50, v/v) at a concentration of $6 \times 10^{-5}M$, giving test solutions at final concentration of 75,37. 5, 15, and 7.5 $\mu g/mL$.		
Allelopathic activity	<i>E. helioscopia</i> leaves were dried powdered and extracted in distilled water and four different organic solvents, i.e. methanol, ethyl acetate, acetone and n-hexane, by using Soxhlet extractor	In vivo	Allelopathic effects of <i>E. helioscopia L.</i> on the growth of lettuce seeds were studied;	Control: without treatment	Different concentrations, i.e. 2%, 4% and 6% of five different solvents (aqueous, methanol, ethyl acetate, n-hexane and acetone) were used against the growth of test plant.	All extracts' concentrations exhibited a variable inhibitory effect on lettuce germination. Extract of <i>E. helioscopia L.</i> inhibited 8–9% radicle and 11% hypocotyl growth	[99]
Anticancer activity	Ethyl acetate extract (EAE) of <i>E. helioscopia</i>	In vivo: mice	To evaluate EAE to treat nude mice xenografts of human HCC and investigated its effect on tumor progression with regard to growth, apoptosis, invasion, and metastasis.	Control: without treatment	The EAE was mixed with sterile water, at a concentration of 1 $\mu g/m$, 50 $\mu g/mL$, 100 $\mu g/mL$, 200 $\mu g/mL$.	EAE could effectively inhibit tumor growth, induce apoptosis, and inhibit tumor invasion and metastasis in vivo; it is suggested that EAE is a potential candidate for as a new anticancer agent.	[92]
Anti-nociceptive, anti-inflammatory and anti-pyretic activities	Latex and leaves methanol extract of <i>E. helioscopia L.</i>	In vivo: mice	To evaluate effects of latex and leaves methanol extract of <i>E. helioscopia L.</i> against chemical (acetic acid induced writhing and formalin tests) and thermal pain stimuli (hot plate test), carrageenan induced paw edema and brewer's yeast induced pyrexia in mice respectively.	Group I: Control without treatment; Group II: standard Brufen, 100 mg/kg, orally; Group III: standard Tramadol, 10 mg/kg, orally; Groups IV-VI: Treated with aqueous solutions of L.MT (100, 200 and 300 mg/kg, orally respectively	Leaves methanol extract and latex were administered to mice, orally at doses, 100, 200 and 300 mg/kg.	<i>E. helioscopia L.</i> possesses marked anti-nociceptive, anti-inflammatory and anti-pyretic activities that can be attributed to the inhibition of synthesis of prostaglandins and other mediators responsible for pain, inflammation and pyrexia.	[15]
Antibacterial activity	Ethanol extract of the whole plant of <i>E. helioscopia L.</i>	In vitro	To evaluate the antibacterial activity of the compounds from the whole plant of <i>Euphorbia helioscopia L.</i>	DMSO, the solvent for compound 1 , was employed as the negative control and triclosan (MIC 3.9, 3.9 $\mu g \cdot mL^{-1}$) was used as positive control.	Antibacterial activity was tested with the 5 $\mu g/dics$ of the test compound using Whatman No. 1 sterile filter paper discs (6 mm).	Euphoheliosnoid E showed significant antimicrobial activity against oral pathogens.	[77]
Antileishmanial	Air-dried and	In vitro	To screened its	DMSO or	2 ; 50 & 200 μL	<i>Euphorbia</i>	[100]

Activity	powdered plant material was extracted under shaking at room temperature with MeOH.		antileishmanial activity against <i>Leishmania amazonensis</i> .	pentamidine	of extracts.	<i>helioscopia</i> showed antileishmanial activity with LC50 between $12.5-26.9 \mu\text{g/mL}$ and acceptable selectivity indices of 8–5.	
Catalytic activity	Aqueous extract of dried powder of <i>E. helioscopia L.</i> leaves	In vitro	To study Catalytic activity of Ag NPs for the synthesis of propargylamines.	Control without catalyst	–	Synthesis of silver nanoparticles (Ag NPs) using <i>E. helioscopia L.</i> Linn leaf extract for the synthesis of propargylamines, exhibits high catalytic activity.	[101]
Vasodepressor activity	5,11-jatrophadiene-3-benzoyloxy-7,9,14-triacetyloxy-15-ol and 2 derivatives of lupane, lup-20 (29)-ene-3-acetate and lup-20 (29)-ene-3-palmitate, as well as common triterpenoids of <i>Euphorbiaceae</i> , 24-methylene cycloartanol, 24-methylene-cycloart-3-one, cycloartanol and stigmast-4-en-3-one were isolated from <i>E. helioscopia L.</i>	In vivo : Mice	To extract secondary metabolites of <i>E. helioscopia L.</i> and evaluate their vasodepressor activity.	Control group (n = 6) received ethanol diluted 25% with saline solution.	Test group (n = 6) received 2 mg / kg intravenous doses of single compounds.	Euphornin (1), lup-20 (29)-ene-3-acetate (2) and stigmast-4-en-3-one (7) showed a significant vasodepressor effect.	[3]
Antifeedant and cytotoxic activities	Dried and powdered whole plant of <i>E. helioscopia</i> was extracted with EtOH at room temperature.	Cytotoxic Assay: In vitro Antifeedant Activity: The insect cotton bollworm (<i>Helicoverpa armigera</i>)	To evaluate Antifeedant and cytotoxic activities of euphoscopoids A-C.	Cytotoxic Assay: Taxol was used a positive control Antifeedant Activity: Commercial neem oil was used as positive control.	Cytotoxic Assay Compounds were added at a dosage of 0.128 – 80 μM . Antifeedant Activity: Compound was tested in five different concentrations, started from 62.5 to 1000 $\mu\text{g/mL}$.	All compounds showed significant antifeedant activity against a generalist plant-feeding insect, <i>Helicoverpa armigera</i> , with EC_{50} values ranging from 2.05 to 4.34 $\mu\text{g/cm}^2$. In addition, compound 2 showed moderate cytotoxicity against tumor cell lines NCI-H1975, HepG2 and MCF-2,	[53]

						while compounds 1 and 3 were not active at 80 μ M.	
Antimicrobial activity	<i>E. helioscopia</i> L. powder was extracted by percolation in 95% ethanol at room temperature for two days.	In vitro	To evaluate antimicrobial activity of <i>E. helioscopia</i> L. extracts.	Two control tubes, containing the growth medium, saline and the inoculum were maintained	Plant extracts were tested in a concentration of 100 mg/ml and incubated at 37 °C for 24-48 h (bacterial strains) and at 25 °C for 3-5 days (fungal strains).	<i>E. helioscopia</i> L. extracts were active against bacterial and fungal test organisms especially against <i>Klebsiella pneumonia</i> , <i>Staphylococcus aureus</i> , <i>S. epidermidis</i> , <i>Microsporium canis</i> and <i>Geotricum candidum</i> ,	[93]
Antimicrobial and anticancer activity	The AgNPs were biosynthesized from the leaves extract of <i>E. helioscopia</i> L. under mild reaction conditions without the need for high temperature, extensive organic solvents or surfactants.	In vitro	To biosynthesize of silver nanoparticles (AgNPs) and AgNPs-loaded chitosan-alginate constructs using methanolic leaves extract of <i>E. helioscopia</i> . with antimicrobial and anticancer potentialities	Antimicrobial activity: Without treatment anticancer activity: Cells without AgNPs and AgNPs loaded chitosan alginate constructs supplement were considered as a control	anticancer activity: Cells were incubated with 20 μ L of MTT (5 mg/mL in PBS) in fresh medium for 4 h at 37 °C.	Antimicrobial activity: The antibacterial activities of AgNPs and AgNPs loaded chitosan-alginate constructs were tested against six bacterial strains i.e. <i>Staphylococcus aureus</i> , <i>Pseudomonas aeruginosa</i> , <i>Klebsiella pneumoniae</i> , <i>Acinetobacter baumannii</i> , <i>Morganella morganii</i> and <i>Haemophilus influenza</i> . A significant reduction in the log values was recorded for all test constructs, in comparison to the initial bacterial count (control value, i.e., 1.5×10^8 CFU/mL). anticancer activity: The cytotoxicity profile revealed complete biocompatibility against normal cell line i.e. L929. Almost all constructs showed considerable	[91]

						cytotoxicity up to certain extent against human epithelial cells (HeLa) cancer cells.	
P-glycoprotein (P-gp) inhibitory and cytotoxic activities.	The dried and powdered whole plants of <i>E. helioscopia</i> L. were exhaustively extracted with 80% EtOH under reflux.	In vitro	To evaluate biological evaluation of Helioosterpenoids A and B	Positive control : Cyclosporin A (CsA)	Compounds were tested at 0.5, 1.0, 2.5, 10 and 20 μ M.	Helioosterpenoids A and B were found to be potent inhibitors of P glycoprotein (ABCB1) and Helioosterpenoids A also exhibited cytotoxicity against MDA-MB-231 cell lines.	[84]
Antiviral activity	The dried and powdered whole plants of <i>E. helioscopia</i> L. were exhaustively extracted with 80% EtOH under reflux.	In vitro	To evaluate biological effects of <i>E. helioscopia</i> L. extracts.	positive control: Acyclovir (ACV)	-	Secoheliosphanes B showed modest activity against HSV-1 with IC50 value of 6.41 μ M.	[64]
Antitumor activity	The air-dried and powdered <i>E. helioscopia</i> L. were extracted with 95% EtOH three times.	In vitro	To evaluate antitumor activity of <i>E. helioscopia</i> L. extracts.	CCCK8 kit	Concentrations for screening assay was 10 μ M and for dose-dependent apoptotic activity assay were 1 μ M, 2 μ M, 5 μ M, 10 μ M, 20 μ M, and 40 μ M.	Two triterpenes named euphorbatrine increased Hela ^{-/-} cell death via activating apoptosis pathway other than necroptosis, with EC50 values of 1.59 \pm 0.25 and 26.48 \pm 0.78 μ M, respectively, which therefore may account for the therapeutic use of <i>E. helioscopia</i> L. the treatment of tumor in folk.	[68]
Lipid-lowering activity	Air-dried and powdered <i>E. helioscopia</i> L. was extracted with 95% EtOH three times at room temperature and concentrated in vacuo.	In vivo: hamsters	<i>E. helioscopia</i> L. extracts were established to screen for potential lipid modulators.	Control without treatment.	Treatment Group (n=6), administered CMC-Na or Euphornin L compound (30 mg/kg) daily in an intragastric manner respectively for 18 days.	Euphornin L, a relatively abundant chemical in <i>E. helioscopia</i> L., showed remarkable lipid-lowering effect in vivo, which makes it a promising lead for development of new lipid-lowering agents	[62]
Multidrug resistance modulators	The air-dried and powdered <i>E. helioscopia</i>	In vitro	To evaluate MDR reversal activities of the	Positive control : Verapamil	Tested concentrations (2 μ M and 20 μ M)	Inhibition ratios of all compounds	[78]

activity	<i>L.</i> were extracted with 95% EtOH at room temperature and concentrated to give a crude extracted.		compounds against the K562/ADR cells were measured using a MTT assay.			were less than 50% at 2 μ M and only two compounds (euphornoate B and C) exhibited cytotoxic (inhibition ratios were more than 50%) at 20 μ M. and almost all tested compounds' reversal abilities were greater than the positive control	
Anti-cancer activity	Qiyusanlong (QYSL) decoction was composed of 10 variants of Chinese medicine including <i>Astragalus membranaceus</i> (Huangqi), <i>Polygonatum odoratum</i> (yuzu), <i>Scolopendra</i> (tianlong), <i>Pberetima</i> (dilong), <i>Solanum nigrum</i> (longkui), <i>Herbahedyotis</i> (baihushecao), <i>Semen coicis</i> (yiyiren), <i>Euphorbia helioscopia</i> (zeqi), <i>Curcuma longa</i> (eshu) and tendrill-leaved fritillary bulb (chuanbei).	In vivo: mice	To study effects and function of Qiyusanlong (QYSL) decoction	Control group: Mice received dosage of 0.2 ml/10 g physiological saline via intragastric administration for 21 days, and 0.4 ml of physiological saline by intraperitoneal injection once a week.	- 20.12 g/kg QYSL decoction for 21 days, and 0.4 ml physiological saline via intraperitoneal injection once a week. - 40.24 g/kg QYSL for 21 days, and 0.4 ml physiological saline via intraperitoneal injection once a week. - 80.48 g/kg QYSL for 21 days, and 0.4 ml physiological saline via intraperitoneal injection once a week.	Results revealed the function of QYSL decoction as a lung cancer treatment and provided insight for a novel lung cancer therapy.	[94]
Cytotoxic activity	Ethanollic extract of <i>E. helioscopia L.</i>	In vitro	To evaluate cytotoxic activity of Ethanolic extract of <i>E. helioscopia L.</i>	Positive control: Gemcitabine (IC50 59.2 nM on PANC-1)	-	Results showed eupheliolides F and L had significant cytotoxic activity against MCF-7 (IC50 9.5 and 9.8 mM, respectively) and PANC-1 (IC50 10.7 and 10.3 mM, respectively) cells.	[86]
Antifungal activity	Leaves of <i>E. helioscopia L.</i> were extracted with distilled water	In vitro	Nanoparticles of CuO and Fe2O3 fabricated using leaves extract of <i>E. helioscopia L.</i> were used to	Positive control: Hexahit 0.1 mg/ml (20 μ l/disc)	Different concentrations were used 25 μ l, 50 μ l, 75 μ l of 0 (.10 mg/ml NPs)	Iron oxide nanoparticles using leaves extract of <i>E. helioscopia L.</i> exhibit greater	[95]

			prevent the growth of fungus -Cladosporium herbarum			antifungal activities against the <i>Cladosporium herbarum</i> as compared to copper oxide nanoparticles.	
Triglyceride-lowering activity	Ethanollic extract of the whole plants of <i>E. helioscopia L.</i>	In vitro	To evaluate triglyceride-lowering activity of Euphorhelipanes A and B	positive control : clinic lipid-lowering drug rosuglitazone	1–50 µM	Euphorhelipanes A and B showed a triglyceride-lowering effect in oleic-acid-stimulated HuH7 cells at concentrations of 1–50 µM	[8]
Anti-inflammatory Activity	The air-dried aerial parts of <i>E. helioscopia L.</i> were powdered and extracted with 95% EtOH (room temperature) three times. After being suspended in water, the combined extract was partitioned with petroleum ether, ethylacetate, and n-butanol, successively.	In vitro	To evaluate Anti-inflammatory Activity of <i>E. helioscopia L.</i> extarcts.	Positive controls: Cajaninstilbene acid and dexamethasone	Inhibition ratios of 30.19 ± 4.09% and 34.25 ± 4.01%, respectively, at 15 µM	Heliojatrone C showed an IC50 of 7.4 ± 0.6 µM, which might be related to the regulation of the NF-κB signaling pathway by suppressing the translocation of the p65 subunit and the consequent reduction of IL-6 and TNF-α secretions.	[82]

Toxicity

Some herbal products are sold as non-toxic food supplements or popular drugs. However, this is not always true, especially if taken as over-the-counter medications, or used in combination with other herbs. In addition, they can have adverse effects, such as stimulation and hallucinogenic properties [102, 103]. Nevertheless, these products are readily available and have widespread use. A large variety of dietary supplements to lose weight are marketed with claims of effectiveness [104-105, 106]. The lack of data on toxicity and/or efficiency of many ingredients of these products, even the predominant ingredients, are worrying an alarming [107-108, 109].

Studies in vivo and in vitro were conducted to evaluate the potential toxicity of *E. helioscopia L.*, their extracts or their association with other ingredients (Table 4). *E. helioscopia L.* caused several irritant contact dermatitis or allergic contact dermatitis, as a result of direct contact [25]. 12-dioxyphorbol-13-phenylacetate-20-acetate has been shown to be the major component of the toxic fraction and the most irritating substance [110, 111].

Molluscicidal activity is widespread in *Euphorbiaceae* family, although the activity varies considerably from one species to another and even between different parts of the same plant [4-23, 24]. Al-Zanbagi studied in 2000 *E. helioscopia L.* with two other plants from *Euphorbiaceae* family, from Saudi Arabia, to identify those parts of plants that had molluscicidal activity against the snail *Biomphalaria pfeifferi*. By 2005, she found that very low concentrations of fresh leaf extracts of methanol and acetone extracts of *E. helioscopia L.* were effective for killing the snail with LC50 = 8.9 ppm. The same in other study results showed that acetone extract of *E. helioscopia L.* was the most toxic extract of both *C. Papiens* larvae and *B. Alexandrina* snails. In addition pellets formulated from stems and leaves of *E. helioscopia L.* showed molluscicidal activity against molluscs, *A. Hortensis* and *T. Pisana*. *E. helioscopia L.* aqueous extract severely affected the germination of wheat (*Triticum Aestivum L.*) and pea (*Pisum Sativum L.*), by reduction of plumule and radicle length, as well as their fresh and dry masses.

Therefore, for toxicity testing, it is important to determine the dose of the drug, bearing in mind the form of pharmaceutical preparation of its extract and to specify the administered amount, particularly in vivo tests, where the weight of the animal is taken in to account. In addition to the numerous pharmacological benefits and useful therapeutic indications for humans, *E. helioscopia L.* has demonstrated toxicological potential, especially as skin irritant (Table 4).

Table 4: *Euphorbia Helioscopia's* toxicity

Toxicity	Details of the extract	In vivo / in vitro test	Objective	Control used	Dose tested for drugs	Findings	Ref.
Phytotoxicity	Aqueous extract of <i>E. helioscopia L.</i>	In vivo: wheat (<i>Triticum Aestivum L.</i>) and pea (<i>Pisum Sativum L.</i>).	To evaluate the phytotoxicity of <i>E. helioscopia L.</i> on wheat (<i>Triticum Aestivum L.</i>) and pea (<i>Pisum Sativum L.</i>).	Control (distilled water)	(1.0%, 2.5%, 5.0% and 10%).	<i>E. helioscopia L.</i> aqueous extract showed several reduction in germination, plumule and radicle length, as well as their fresh and dry masses.	[21]
Molluscicidal activity	Methanol and chloroform extracts of <i>E. helioscopia L.</i>	In vivo: Snails, <i>Biomphalaria Pfeifferi</i> .	To evaluate molluscicidal activity of different part fresh and dried of three plants from the family <i>Euphorbiaceae</i> from Saudi Arabia.	Controls were prepared in 1litre beakers using dechlorinated tap water.	10 different concentrations (10, 20, 30, 40, 50, 60, 70, 80, 90 and 100 ppm).	For fresh material, the best extracts were: acetone extract of the fresh leaves of <i>J. Glauca</i> , hexane extract of fresh stems of <i>E. helioscopia L.</i> and chloroform extract of the fresh leaves of <i>E. Schimperiana</i> . For the dry material, the best extracts were: chloroform extract of the dry leaves of <i>J. Glauca</i> , methanol extract of the dry leaves of <i>E. helioscopia L.</i> and methanol extract of the dry stems of <i>E. Schimperiana</i> . Dry leaf and stem extracts were the most effective with LD ₅₀ values ranging from 7.6 to 50.8 ppm and that of LD ₉₀ from 11.8 to 68.2 ppm.	[23]
Molluscicidal activity	Extracts from fresh leaves of <i>E. helioscopia L.</i> with: Cold water, Hot water, Methanol, Chloroform, Acetone, Hexane.	In vivo: snails: <i>Bulinus wrighti</i>	To evaluate molluscicidal activity of <i>E. helioscopia L.</i> extracts against the snail <i>Bulinus wrighti</i>	<i>Bulinus wrighti</i>	Without treatment	Very low concentrations of fresh leaf extracts were effective in killing the snail. The LC ₅₀ of methanol and acetone extracts for <i>Euphorbia helioscopia</i> was 8.9 ppm.	[24]
Allergic contact dermatitis	<i>E. helioscopia L.</i> related contact dermatitis (Irritant contact dermatitis or allergic contact dermatitis)	In vivo : kids	To share experience with <i>Euphorbia Helioscopia</i> contact dermatitis in emergency department.	-	-	Contact surface can be washed with water. There is no need any drugs for treatment of <i>Euphorbia Helioscopia</i> contact dermatitis.	[25]
Skin irritant	Four ester of 12-dioxyporphol were isolated from the fresh aerial parts of <i>E. helioscopia L.</i>	In vivo: rates	Isolation of diterpene esters together with assessments of the irritant ³² potencies of pure toxins	Without treatment	Five microlitre doses were applied as before to mice ears.	12-dioxyporphol-13-phenylacetate-20-acetate was found to be the major component of the toxic fraction and was the most irritant substance	[111]

Toxic phytodermatitis	A 6-year-old patient presented with linear erythema and bullae on the face. The lesions developed after playing with plants the day before. The plant was identified as <i>Euphorbia Helioscopia</i> .	In vivo	To sensitize that The sun spurge belongs to the <i>Euphorbiaceae</i> plant family. These plants produce a typical milky juice that causes toxic reactions following contact with skin and mucous membranes.	-	-	The exact determination of the causative plants is a prerequisite for the diagnosis of phytodermatitis.	[112]
Molluscicidal activity	Pellets containing leaves, flowers, stems and roots of <i>E. helioscopia L.</i>	In vivo: snails: <i>Theba Pisana</i> and slugs <i>Arion Hortensis</i>	To test and evaluate pellets toxicity containing roots, stems, leaves or flowers of <i>E. helioscopia L.</i> against adults of <i>Theba Pisana</i> and <i>Arion Hortensis</i> .	Positive control: Ariotox (5% metaldehyde) as granules used at the recommended rate (20 kg / ha); Negative control: Contained sucrose, 10mM starch and amino acids (20mM arginine) in a 100ml solution of 2% agar formed as pellets.	Concentrations of 0.25; 0.5; 0.7; 1 or 2 g per 100 ml of 2% agar of each organ of the plant were mixed with sucrose, 10 mM starch and amino acids (20 mM arginine) in a 100 ml solution of agar 2% formed as pellets.	Formulated pellets from stems and leaves of <i>E. helioscopia L.</i> showed molluscicidal activity against the tested molluscs, <i>A. Hortensis</i> and <i>T. Pisana</i> .	[4]
Insecticidal and molluscicidal activities	Extract of <i>E. helioscopia L.</i> (<i>Euphorbiaceae</i>), <i>Calendula Micrantha</i> (<i>Compositae</i>) and <i>Azadriachta Indica</i> (<i>Meliaceae</i>) with petroleum ether, benzene, acetone, chloroform, ether, acetate of ethyl and methanol.	In vivo: larvae of <i>Culex Papiens</i> and snail <i>Biomphalaria Alexandrina</i>	To evaluate the effect of a few extracts of three plants: <i>E. helioscopia L.</i> , <i>Calendula Micrantha</i> and <i>Azadriachta Indica</i> on both snails of <i>Biomphalaria Alexandrina</i> and <i>Culex Papiens</i> first instar larvae.	Control : 0.05% of ethanol	10 - 500 ppm	Acetone extracts of the three tested plants were the most active. The similarity of the data of all the fractions tested on both species revealed that these plant extracts probably have the same mode of action against tested pests.	[22]
Contact dermatitis	The whole <i>E. helioscopia</i> plant.	In vivo: Two girls, aged 4 years and 5 years.	To report blistering lesions and toxic reactions after contact with the skin and mucous membranes caused by <i>E. helioscopia</i>	-	-	<i>E. helioscopia</i> constitute a risk to children, who may be exposed to the sap during play, and to those who may be exposed when the plants are used in traditional medicine.	[113]
Irritant contact dermatitis	The whole plant of <i>E. helioscopia L.</i>	In vivo: three patient	To examine the phytodermatitis cases caused by plants	-	-	12-deoxyphorbol-13-phenylacetal-20-acetate is compound responsible of irritant contact dermatitis	[114]

CONCLUSION

Plus than one haundred references were used to prepare this work that gather as well recent and old conducted studies that aim to determine the different possible uses/proprieties of *E. helioscopia L.* These proprieties can be classified as chemical, pharmacological and toxic ones. A resume of objectives, used methodologies and main results is presented by type of propriety. Various biological and therapeutic activities of *E. helioscopia L.* have been reported in the literature. Effectiveness of the different classes of secondary metabolites isolated from this plant was confirmed by a wide range of experiments referred in this review. The use of this plant in certain biological and therapeutic applications requires determination of relevant concentrations and economic gains via biological reactor tests. Although a large number of studies were conducted on the determination of *E. helioscopia L.* different proprieties, series of assessments are needed to establish the limits of their environmental safety. Extracts from *E. helioscopia L.* have shown sufficient activity to warrant further investigation as possible biomolluscicides. The study of natural products of this plant could lead to the discovery of new structures that could serve as a basis for different future products.

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